4953-6

THE AMERICAN REVIEW OF TUBERCULOSIS

JOURNAL OF
THE NATIONAL TUBERCULOSIS ASSOCIATION

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VOLUME XXX
JULY-DECEMBER, 1934

10,048
41 V. 30, 1934
3/21/35

PUBLISHED MONTHLY
AT MT. ROYAL AND GUILFORD AVENUES, BALTIMORE, MD.
BY THE NATIONAL TUBERCULOSIS ASSOCIATION

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THE INCIDENCE OF TUBERCULOUS INFECTION AMONG CHILDREN IN NEW YORK CITY

A Survey of 14,699 Children Tuberculin-Tested in Hospitals or Attending Clinics, Three-Year Period, 1930–1932[1]

GODIAS J. DROLET[2]

INTRODUCTION

Recently Myers (1) pertinently wrote

> Is it not time that the medical profession made some investigation throughout this country to determine whether the figures so often quoted concerning the incidence of tuberculosis are true? . . . . Two generations have grown up since some of the necropsy studies were made, and one since the original tuberculin tests were administered. . . . . Is the tuberculin test positive in as high a percentage as it was then?

Also, Dickey and Seitz (2), in connection with their study of the incidence of tuberculous infection among San Francisco children, concluded that "frequent surveys of representative cross-sections of the child population in all communities would be valuable to show the changing conditions of exposure."

In New York City, the Commissioner of Health, Dr. S. W. Wynne, as president of the Association of Tuberculosis Clinics of Greater New York, appointed a short while ago a Committee[3] to study further the question of tuberculosis in children and to offer practical recommendations toward its control.

[1] From records in hospitals, by courtesy of Doctors H. W. Dargeon, L. C. Schroeder, C. H. Smith; and, in clinics, of Doctors H. Bakwin, M. W. Barnard, H. Chaplin, J. Heitlinger and D. Ulmar. Special thanks are also due to Doctor D. C. Martin of the Tuberculosis Division and Miss Amelia Grant of the Nursing Bureau of the Department of Health of the City of New York for the assistance rendered by them and members of their staffs in the study of their records.

[2] New York Tuberculosis and Health Association.

[3] The Committee, still sitting, is composed of the following physicians: G. G. Ornstein, Chairman; J. B. Amberson, Jr.; M. W. Barnard; W. Grethman; H. E. Kleinschmidt; D. C. Martin; W. H. Park; B. Schick; and C. H. Smith. Also, as Secretary, Miss M. E. Higgins and, as Statistician, G. J. Drolet.

It was to assist the committee just mentioned and to answer in particular questions as to the present prevalence of tuberculous infection in New York City, as well as its fatality, that records of children tested with tuberculin intracutaneously were assembled for the years 1930, 1931 and 1932 from two groups of institutions: the first, drawing from the general population, consisted of three general hospitals and seven special clinics (baby health stations, preschool clinics, health-centre examination services, etc.); the second covered the children's sections in eight tuberculosis clinics scattered in the four more populous boroughs of Metropolitan New York.

With a grand total of 41,807 persons known to the Health Department as suffering from tuberculosis during the year 1921, and 31,621, or ten thousand fewer, in the year 1931, why should we assume that dissemination of tubercle bacilli is on the same scale at present as formerly? With an increasingly effective control of home sources of tuberculosis, especially in the city; with more than twelve thousand patients rushed annually to tuberculosis hospitals and sanatoria, whether they are bed-cases or not:—why assume that the prevalence of tuberculous infection has remained constant? Many records are now available showing a large proportion of children, and even of adolescents, as yet uninfected with tuberculosis during the first twenty years of their lives. Why accept that twenty years later all must be infected?

HOSPITAL SERIES

To ascertain the present prevalence of tuberculous infection in New York City where it might be greatest, naturally in the older and more congested borough of Manhattan, as well as to secure representative data especially among very young children, since results of surveys of those of school-age are now common, the records[4] of the Children's Medical Division at Bellevue Hospital, of the New York Nursery and Child's Hospital, and of St. Luke's Hospital were utilized.

Bellevue, the large and well-known municipal institution, is located on the East Side, and its clientele is drawn widely from the poorer districts; 3,730 histories of children admitted there during 1930 and in 1931 were studied for this investigation. Of the children, 2,528 or slightly

[4] Very graciously made available by Doctor Charles Hendee Smith, for Bellevue; by Doctor Louis C. Schroeder, for Nursery and Child's; and by Doctor Harold Dargeon, for St. Luke's.

more than two-thirds were under five years of age. And, it should be added that about 7 per cent of all the children there, at least in 1931, were colored.

On the West Side, at the Nursery and Child's Hospital, a private institution, but also serving a poor district, 682 records for the year 1931 were obtained; practically all, namely 94 per cent, were of children under five years of age, and some 27 per cent were colored.

At St. Luke's Hospital, a private institution, on the upper, and comparatively better-off, section of the West Side, 1,668 records of admissions for the years 1930, 1931 and 1932 were taken. Of the children there, 49 per cent only were under five years of age; 38 per cent, five to ten years old; and, 13 per cent, ten to fifteen years. Also, of all children at St. Luke's, only 6 per cent were colored.

Altogether, therefore, 6,080 records were scanned for the results of tuberculin-testing, intracutaneous method, generally repeated with higher dosage[5] when negative at first, and in institutions where conditions for continuous observation were naturally better;—at least as compared with those prevailing during surveys among children in out-patient or clinic services, or in schools where certain reactions may be missed and, for that matter, some children may fail to return.

Age

As shown in table 1, considering all ages, only 13.7 per cent reacted positively: 4.3 per cent of the babies under one; 9.3 per cent of all those under five years; 19.1 per cent of those five to ten; and 29.2 per cent of those ten to fifteen years old. Classified by hospital (bearing in mind the

[5] Specifically, the dosage for the Bellevue Hospital group of children (3,730 out of the 6,080, or 61 per cent of all those tested in this series) began at 0.05 mgm. and, if negative, was run up in five steps to 2 mgm. "As a rule, only two tests are made," says C. Hendee Smith, and "it is a rare occurrence to obtain a positive reaction at the second or later tests when the first is negative."

In St. Luke's Hospital, the 1,668 children (28 per cent of the entire group covered in the hospital series) were tested usually once with 0.1 mgm.

At the Nursery and Child's Hospital, with the 682 children (only 11 per cent of the hospital series, and where the great majority were very young, namely, 639, or 94 per cent, under five years of age) the dose was only 0.01 mgm., repeated among negatives with "higher dosage where symptoms, signs or testing led to suspicions of possible tuberculosis."

As a matter of fact, using a hundredth of a milligram among those under five years, the percentage of reactors, namely, 7.7, at the Nursery and Child's, was slightly higher than at St. Luke's, where it was 6.7 per cent, even after using 0.1 mgm. At Bellevue (drawing from an undoubtedly lower economic group) the children of the same age, which included some Porto Ricans, furnished, on repeated tests, a total of 10.6 per cent reactors.

different age-distribution and the higher proportion of colored at the Nursery and Child's) the positive reactions averaged 16 per cent at Bellevue, 7 per cent at Nursery and Child's, and 11 per cent at St. Luke's. Qualified for age, in Bellevue, Nursery and Child's, and St. Luke's, respectively, reactions ran as follows: children under five, 11

TABLE 1

Intracutaneous tuberculin tests among 6,080 children admitted to three general hospitals, New York City, 1930–1932

AGE	MALE			FEMALE			TOTAL		
	Tested	Positive		Tested	Positive		Tested	Positive	
		Number	Per cent		Number	Per cent		Number	Per cent
0– 3 mos.	367	6	1.6	288	4	1.4	655	10	1.5
3– 6 mos.	258	8	3.1	189	4	2.1	447	12	2.7
6–12 mos.	407	35	8.6	280	20	7.1	687	55	8.0
1– 2 yrs.	442	38	8.6	345	33	9.6	787	71	9.0
2– 3 yrs.	334	44	13.2	264	42	15.9	598	86	14.4
3– 4 yrs.	241	31	12.9	202	38	18.8	443	69	15.6
4– 5 yrs.	183	34	18.6	179	34	19.0	362	68	18.8
5– 6 yrs.	174	26	14.9	131	22	16.8	305	48	15.7
6– 7 yrs.	176	30	17.0	155	25	16.1	331	55	16.6
7– 8 yrs.	156	24	15.4	143	28	19.6	299	52	17.4
8– 9 yrs.	162	33	20.4	142	33	23.2	304	66	21.7
9–10 yrs.	140	28	20.0	127	38	29.9	267	66	24.7
10–11 yrs.	141	44	31.2	124	34	27.4	265	78	29.4
11–12 yrs.	119	34	28.6	118	37	31.4	237	71	30.0
12–13 yrs.	45	8	17.8	36	12	33.3	81	20	24.7
13–14 yrs.	3	0	0.0	6	3	50.0	9	3	33.3
14–15 yrs.	2	1	50.0	1	1	100.0	3	2	66.7
0– 1 yr.	1,032	49	4.7	757	28	3.7	1,789	77	4.3
0– 5 yrs.	2,232	196	8.8	1,747	175	10.0	3,979	371	9.3
5–10 yrs.	808	141	17.4	698	146	20.9	1,506	287	19.1
10–15 yrs.	310	87	28.1	285	87	30.5	595	174	29.2
0–15 yrs.	3,350	424	12.7	2,730	408	14.9	6,080	832	13.7

per cent, 8 per cent and 7 per cent; and for those five to ten years old, 24 per cent, 29 per cent and 14 per cent.

Among infants under one only, positive reactions were highest at Nursery and Child's (with many colored children there); namely, 6 or 8 per cent, depending on sex, and lowest at St. Luke's, 3 or 4 per cent. At Bellevue, the reactions among infants shaded slightly higher than at the last mentioned place, namely, 3.3 and 4.2 per cent.

Sex

By sex, first it should be noticed, somewhat as usual in sickness or mortality records of the very young, that more boys than girls were in the hospitals, 3,350 against 2,730. Positive reactions averaged, for male children of all ages, 13 per cent, and for female children, 15 per cent; among babies under one, in the same order of sex, 5 against 4 per cent; among all those under five, 9 per cent of the boys and 10 per cent of the girls; among those five to ten, 17 against 21; and, among those ten to fifteen, 28 compared with 31. For sex, therefore, here as elsewhere no really significant difference was found as to the proportion which are infected during childhood.

After all, opportunities for exposure, in a big city, in crowded tenements, congested streets, enormously large schools, at "movies," in overpacked subways and other means of transportation, are all too ever-present and surrounding everyone too much to expect anything but such a common result here. And yet, let it be not forgotten, when trying to interpret the clinical significance of tuberculous infection, that mortality rates from this disease vary markedly in the two sexes at several important periods of life, in infancy and in old age, as well as in the adult years.

Color

By color, information was available for most of the children at each of the three hospitals, but at Bellevue Hospital this item was utilized only with the admissions for the year 1930. Notwithstanding, distinction as to color was noted upon 3,933 records; 3,530 children were white and 403, or nearly 12 per cent, were colored,—a goodly proportion of the latter since in New York City Negroes are approximately but 5 per cent of the total population, though they furnish 20 per cent of all the tuberculosis mortality.

As may be studied in part A of table 2, 11.1 per cent of the white children reacted positively and 15.4 per cent of the colored. The differences between the two races were however greater among the very young: 12 per cent of all the colored under five years reacted, compared with 7 per cent among the white of the same age; and, 8.2 per cent of the Negro infants to 3.4 of the white ones. (See also table 6 in the tuberculosis clinic series for differences as to color.)

Only minor differences in reactions according to color, especially when large groups of children are considered, have usually been reported by

most observers, and these in no wise explain the wide variations in the death-rates from tuberculosis of colored and white children. Thus, for instance, in the United States Registration Area during the year 1929, among white baby boys under one the tuberculosis death-rate was 48 per 100,000 for that age and that of the colored infant boys 106, or 2.2 times that of the white. Among those one to five years old, the colored

TABLE 2

Intracutaneous tuberculin tests, hospital series, New York City, 1930–1932

A. According to color, among 3,933 children in three general hospitals

AGE	WHITE			COLORED			TOTAL		
	Tested	Positive		Tested	Positive		Tested	Positive	
		Number	Per cent		Number	Per cent		Number	Per cent
0– 1 yr.	1,035	35	3.4	146	12	8.2	1,181	47	4.0
0– 5 yrs.	2,235	161	7.2	319	39	12.2	2,554	200	7.8
5–10 yrs.	946	140	14.8	59	15	25.4	1,005	155	15.4
10–15 yrs.	349	92	26.4	25	8	32.0	374	100	26.7
0–15 yrs.	3,530	393	11.1	403	62	15.4	3,933	455	11.6

B. According to "history of contact," among 1,668 children in St. Luke's Hospital

AGE	POSITIVE HISTORY OF CONTACT			NEGATIVE HISTORY OF CONTACT			TOTAL		
	Tested	Reacted		Tested	Reacted		Tested	Reacted	
		Number	Per cent		Number	Per cent		Number	Per cent
0– 1 yr.	3	1	33.3	280	8	2.9	283	9	3.2
0– 5 yrs.	15	7	46.7	797	47	5.9	812	54	6.7
5–10 yrs.	15	4	26.7	616	81	13.1	631	85	13.5
10–15 yrs.	7	2	28.6	218	42	19.3	225	44	19.6
0–15 yrs.	37	13	35.1	1,631	170	10.4	1,668	183	11.0

tuberculosis death-rate was 3.6 times that of the white "toddlers"; among those five to ten years old it was 4.3 times as high; and among those ten to fifteen years it was six times (or 500 per cent higher). As with boys, similar excesses in the mortality rates of colored girls compared with those of white girls are also found. Even still higher ratios in the tuberculosis mortality of colored children to that of the white—some as high as ten times—have been found in New York City. Those

extreme differences cannot be explained on the mere score of varying opportunities for infection, which, in large cities, are fairly common and similar for all racial groups.

Contact

As to "history of contact," the hospital series of children tested carried little information in general. This point, however, was obtained for each of the 1,668 children admitted to St. Luke's Hospital; but only 37 there gave a positive history of home contact with a tuberculosis case. Of the latter 13, or 35 per cent, reacted; and of the 1,631 with "no history of contact," 170, or only 10 per cent, reacted (see part B, table 2). Differences, or excesses, in reactions were, as usual, greatest among the younger children when, of course, intimacy of home contact is greater and going about more limited.

Finally, in this hospital series of children in the heart of New York City, it should be pointed out that up to the age of puberty nearly two-thirds were as yet uninfected with tuberculosis.

Seasonal Influence

As is well known, children's diseases are more prevalent at certain times of the year than at others. In New York City, during the five-year period 1926–1930, the combined registration-rate, among children under fifteen years of age, from measles, scarlet fever, whooping-cough, chickenpox and diphtheria, ranged, during the months of February, March and April, between 4,633 and 5,938 per 100,000 living in that age-group as against 615 to 883 during the months of August, September and October (3). Also, during the same quinquennium, the tuberculosis death-rate for the general population, namely at all ages, averaged 89.4 during March as against 66.4 in October, an excess therefore during the late winter of 35 per cent.

Some have suggested that, at certain times, when general health is better or not so good, and resistance correspondingly higher or lower, reactions may be more frequent or held in abeyance. To test the influence, if any, therefore, of the seasons of the year upon the frequency of the tuberculin reaction among children, the records of those studied in the hospital series, 6,080 under fifteen years of age, were distributed according to the month they were tested. Results are shown in table 3.

There, it may be noted, first, that, whereas in general 14 per cent of the children reacted, the proportions reacting (considering all ages) during

certain months varied only from 12 per cent in January and February to 18 per cent in June. If one groups the data roughly by seasons, namely, June, July and August as summer months, and December, January and February as winter months, the 237 positive reactors among 1,550 in the first instance provide 15 per cent positive compared with 12 per cent in the second instance when there were 173 reactors in the 1,447 tested

TABLE 3

Intracutaneous tuberculin tests among 6,080 children at different seasons in three hospitals, New York City, 1930–1932*

MONTH	AGE											
	0 to 5 years			5 to 10 years			10 to 15 years			0 to 15 years		
	Tested	Positive		Tested	Positive		Tested	Positive		Total	Positive	
		Number	Per cent		Number	Per cent		Number	Per cent		Number	Per cent
January	339	25	7.4	114	22	19.3	31	9	29.0	484	56	11.6
February	244	24	9.8	79	10	12.7	36	10	27.8	359	44	12.3
March	327	32	9.8	118	26	22.0	46	10	21.7	491	68	13.9
April	366	34	9.3	138	29	21.0	58	14	24.1	562	77	13.7
May	360	32	8.9	148	32	21.6	49	17	34.7	557	81	14.5
June	331	37	11.2	110	28	25.5	50	23	46.0	491	88	17.9
July	319	31	9.7	137	23	16.8	46	14	30.4	502	68	13.5
August	334	30	9.0	123	24	19.5	55	18	32.7	512	72	14.1
September	376	38	10.1	134	21	15.7	62	15	24.2	572	74	12.9
October	369	34	9.2	160	35	21.9	58	18	31.0	587	87	14.8
November	326	28	8.6	150	19	12.7	48	11	22.9	524	58	11.1
December	288	26	9.0	95	18	19.0	56	15	26.8	439	59	13.4
Total	3,979	371	9.3	1,506	287	19.1	595	174	29.2	6,080	832	13.7

* Covers 3,730 children admitted to Bellevue Hospital in 1930 and 1931; 682 to the New York Nursery and Child's Hospital in 1931; and 1,668 to St. Luke's Hospital in 1930, 1931 and 1932.

during the colder months,—a rather small, and probably not significant difference.

Even for the small numbers[6] within each five-year age group the range is limited: among children under five years, from 7 to 11 per cent reacted in various months, namely January and June, respectively; among those five to ten years, a range of 13 to 26 per cent in the reactions; and, among those ten to fifteen, from 22 to 46 per cent.

[6] With smaller numbers the probable error, due to mere chance, is correspondingly greater.

CHILDREN ATTENDING SPECIAL CLINICS

The records of nearly two thousand (1,965) other children, all comparatively well (in contradistinction to the 6,080 in the hospitals, all presumably there for some serious illness or injury) were also studied wherever intracutaneous tuberculin tests were known to be routinely done at the present time. These children were attending seven clinics in different sections of the congested East Side in the Borough of Manhattan, New York City, during the year 1932; practically all were from poor families, unable to afford a private physician and, in general, were sent there for a health examination or for observation by visiting nurses of the Department of Health, or by the social workers of welfare societies.

Of the total children tested, 999 attended either the "preschool" or the "children's" clinics of the Bellevue-Yorkville Health Demonstration in East Thirty-eighth Street; and 33, its local baby health-station there. At this place, the prevailing racial groups among the children of the foreign-born are either Irish or Italian. Another three hundred (302) children attended "preschool" clinics of the Department of Health in East Thirty-second and East Nineteenth Streets. A hundred or so (108) came to the Mulberry Health Center, of the Association for Improving the Condition of the Poor, in Mott Street, a very poor Italian district. Finally, 523 were uptown at the East Harlem Health Center, in One Hundred and Sixteenth Street, where many here too were of Italian parentage; here, however, were also included 29 either Porto Rican or Negro children.

Of the total 1,965 "special clinics" children tested with tuberculin, usually with 0.1 mgm., 260, or 13.2 per cent, reacted,—practically the identical proportion as in the hospital group, where 13.7 were found positive (see table 4).

Of the few infants tested, 18 under one year of age, 2 reacted. The largest group, 1,222 under five years of age, furnished 106, or 8.7 per cent, positive reactors; among the 590, five to ten years old, 93, or 15.8 per cent, were positive; and of 153, ten to fifteen, 61, or 39.9 per cent, reacted positively.

Compared with the hospital group, the children attending these "well-baby" or "preschool" clinics showed practically the same proportion, 9 per cent, infected among those under five years of age. Among those five to ten years, the percentage reacting, 16, was slightly less than the 19 for the hospital cases. And for those ten to fifteen, it was higher instead,

—nearly 40 per cent positive at these clinics compared with 29 in the hospital series.

It must be held somewhat surprising to find nowadays among children who have lived, some already for several years, in the poorer and ex-

TABLE 4

Intracutaneous tuberculin tests among 1,965 children attending seven "pre-school" and other clinics, on the East Side of Manhattan, New York City in 1932

AGE	TOTAL TESTED	POSITIVE	
		Number	Per cent
0– 3 mos.	0	0	0
3– 6 mos.	3	0	0
6–12 mos.	15	2	13.3
1– 2 yrs.	82	5	6.1
2– 3 yrs.	452	25	5.5
3– 4 yrs.	337	31	9.2
4– 5 yrs.	333	43	12.9
5– 6 yrs.	260	34	13.1
6– 7 yrs.	118	13	11.0
7– 8 yrs.	82	14	17.1
8– 9 yrs.	68	20	29.4
9–10 yrs.	62	12	19.4
10–11 yrs.	41	15	36.6
11–12 yrs.	39	15	38.5
12–13 yrs.	32	13	40.6
13–14 yrs.	25	12	48.0
14–15 yrs.	16	6	37.5
0– 1 yr.	18	2	11.1
0– 5 yrs.	1,222	106	8.7
5–10 yrs.	590	93	15.8
10–15 yrs.	153	61	39.9
0–15 yrs.	1,965	260	13.2

tremely congested districts of New York City, that such a large proportion are still uninfected with tuberculosis.

CHILDREN ATTENDING TUBERCULOSIS CLINICS

During the three years 1930, 1931 and 1932, in New York City, no less than 131,398 persons[7] were examined at the various tuberculosis clinics

[7] From reports furnished to the writer, as Statistician of the Association of Tuberculo sis Clinics of Greater New York.

that serve every section of the American metropolis. By no means were all these suffering from tuberculosis. Even though 22,936 were diagnosed as clinical cases, 108,462 were at the same time pronounced, by the specialists on duty there, as clinically nontuberculous. As a matter of fact, these chest clinics, many with consultation services for private physicians' cases, are practically the only available public facilities for a "health examination" or for the medical observation of members of families under the care of relief and welfare societies.

The greater proportion of all those seen at the so-called tuberculosis clinics are children under fifteen years of age; the majority of the latter, while not cases of clinical tuberculosis, are however "contacts," namely, from homes or families where there is or was recently a case of tuberculosis. In many instances the primary case, if still with active disease, is apt to be at a tuberculosis hospital or in a sanatorium; but, when his or her children were first examined, it may have been only a short time after the first case was diagnosed.

To ascertain the present amount of infection in this generally exposed group of children, records of more than six thousand (6,429), tested with 0.1 mgm. tuberculin intracutaneously, among those admitted in the three-year period, 1930–1932, were obtained from 8 representative clinics scattered in the four more populous boroughs.

In Manhattan the results of the tuberculin tests of 2,935 children at four clinics were obtained; the positive reactions, 1,476, for all those under fifteen years of age averaged 50.3 per cent. The first clinic studied in that borough was that of Bellevue Hospital on the East Side, limiting itself in this instance, as all district clinics do, to a definite neighborhood. Here 79 per cent of those admitted were "contacts," and the clinic averaged 45 per cent reactors. At the second clinic, Yorkville, serving a district immediately above Bellevue's, on the East Side, and where 69 per cent of the children tested were contacts, 48 per cent of all reacted positively. At the third clinic in Manhattan, St. Luke's, whose district is on the main West Side, and where practically all the children tested were contacts, namely, 96 per cent, and, furthermore, one-third colored, the positive reactors averaged 63 per cent, the highest in the tuberculosis clinic series. The fourth and last clinic studied in Manhattan was that of Harlem Hospital, where 85 per cent of the children tested were colored, and where also contacts made up 89 per cent of the total studied. At this place, in the heart of the largest colored urban section in the United States, and where during the two-year period 1929–

1930, the tuberculosis death-rate was the highest in New York City, namely, 237 per 100,000 population, the children reacting positively were but 50 per cent of the total tested.

In the Borough of the Bronx, at the Mott Haven Clinic, where the majority (79 per cent) of the children were contacts, and mostly white, reactors were 48 per cent of the total.

In the Borough of Queens, at the Jamaica Clinic, with 10 per cent of the children colored, and contacts being two-thirds of all, 44 per cent of the children tested reacted.

In Brooklyn the records of two clinics were studied, those of Prospect and those of Brownsville. The first is somewhat of a general-reference clinic for that large borough; 9 per cent of the children there were colored, and 79 per cent were contacts; positive reactors were found among 58 per cent of all children. At the second Brooklyn clinic, Brownsville, was found the lowest proportion of reactors, 33 per cent. This clinic serves a Jewish district, which has the lowest tuberculosis death-rate of any in New York City, only 36 per 100,000 annually during the two-year period 1929–1930. While the more obvious reason here for such a low percentage of positive reactors is that tuberculosis, at least as far as mortality is an indication, is less prevalent in this section, the fact also that general health here is better and most of the rates for other infectious diseases are lower in this Jewish neighborhood raises the fundamental question of how much resistance or delay to a successful tuberculous implantation a healthier group may offer.

Significant evidence of such a possibility has been offered by Allen (4), who observed, in South Africa, Negro "boys" working in coal- and gold-mines. After carefully testing 418 natives, who had all been in the Witbank Colliery for over a year, the majority of whom had had previous mine-work elsewhere, Allen noticed that of those who retained negative reactions fewer had to be admitted to hospital "for all other diseases" than of those who became positive reactors; thus, of the negative, 13.7 per cent reported sick 19 times; and, of the positive, 20.3 per cent reported 55 times. Allen is inclined to conclude that those with a negative reaction "amongst mine laborers," where "it seemed safe to assume universal exposure to infection," possessed a "higher natural resistance to all diseases, as they seemingly did to tuberculosis."

Still, the two Brooklyn clinics averaged 48 per cent reactors. In fact, considering all of the four more important boroughs of New York, as far as size of population is concerned, the proportion of positive reactors

among "tuberculosis clinic" children varied only from 44 per cent in Queens to 50 per cent in Manhattan. On the other hand, the tuberculosis mortality rates in these same boroughs ranged, for instance, in 1931, from 47 per 100,000 in Queens to 127 in Manhattan.

TABLE 5

Intracutaneous tuberculin tests among 6,429 children admitted to eight tuberculosis clinics in the boroughs of Manhattan, Brooklyn, Bronx and Queens, New York City, 1930–1932

AGE	MALE			FEMALE			TOTAL		
	Tested	Positive		Tested	Positive		Tested	Positive	
		Number	Per cent		Number	Per cent		Number	Per cent
0– 3 mos.	11	3	27.3	14	1	7.1	25	4	16.0
3– 6 mos.	22	3	13.6	26	5	19.2	48	8	16.7
6–12 mos.	51	12	23.5	37	6	16.2	88	18	20.4
1– 2 yrs.	99	31	31.3	101	35	34.7	200	66	33.0
2– 3 yrs.	169	63	37.3	154	64	41.6	323	127	39.3
3– 4 yrs.	197	80	40.6	194	77	39.7	391	157	40.2
4– 5 yrs.	213	97	45.5	234	110	47.0	447	207	46.3
5– 6 yrs.	222	100	45.0	254	112	44.1	476	212	44.5
6– 7 yrs.	269	114	42.4	278	113	40.6	547	227	41.5
7– 8 yrs.	270	116	43.0	264	116	43.9	534	232	43.4
8– 9 yrs.	281	124	44.1	270	135	50.0	551	259	47.0
9–10 yrs.	263	130	49.4	247	134	54.3	510	264	51.8
10–11 yrs.	235	116	49.4	279	143	51.3	514	259	50.4
11–12 yrs.	269	152	56.5	256	145	56.6	525	297	56.6
12–13 yrs.	223	128	57.4	247	147	59.5	470	275	58.5
13–14 yrs.	223	139	62.3	216	144	66.7	439	283	64.4
14–15 yrs.	143	92	64.3	198	136	68.7	341	228	66.9
0– 1 yr.	84	18	21.4	77	12	15.6	161	30	18.6
0– 5 yrs.	762	289	37.9	760	298	39.2	1,522	587	38.6
5–10 yrs.	1,305	584	44.8	1,313	610	46.4	2,618	1,194	45.6
10–15 yrs.	1,093	627	57.4	1,196	715	59.8	2,289	1,342	58.6
0–15 yrs.	3,160	1,500	47.4	3,269	1,623	49.6	6,429	3,123	48.6

For the combined group of the 6,429 children tested in the 8 tuberculosis clinics throughout New York City, details are shown by sex in table 5, for color in table 6, and according to history of contact in table 7. It will be seen that 19 per cent of the infants, generally from tuberculous families, that were tested, were found infected; that of all under five years, 39 per cent reacted; of those five to ten years, 46 per cent; and, of those ten to fifteen, 59 per cent.

Considering the two sexes, all ages, the percentages of positive reactions did not differ significantly: 47.4 per cent among boys and 49.6 per cent among girls.

TABLE 6

Intracutaneous tuberculin tests upon 5,403 children, according to color, among those admitted to six tuberculosis clinics, New York City, 1930–1932

AGE	WHITE			COLORED			TOTAL		
	Tested	Positive		Tested	Positive		Tested	Positive	
		Number	Per cent		Number	Per cent		Number	Per cent
0– 3 mos.	5	0	0	18	4	22.2	23	4	17.4
3– 6 mos.	19	5	26.3	27	3	11.1	46	8	17.4
6–12 mos.	42	7	16.7	33	7	21.2	75	14	18.7
1– 2 yrs.	92	30	32.6	87	31	35.6	179	61	34.1
2– 3 yrs.	185	81	43.8	106	32	30.2	291	113	38.8
3– 4 yrs.	207	87	42.0	131	48	36.6	338	135	39.9
4– 5 yrs.	235	106	45.1	131	62	47.3	366	168	45.9
5– 6 yrs.	268	112	41.8	136	72	52.9	404	184	45.5
6– 7 yrs.	328	125	38.1	131	71	54.2	459	196	42.7
7– 8 yrs.	306	124	40.5	140	73	52.1	446	197	44.2
8– 9 yrs.	330	143	43.3	125	68	54.4	455	211	46.4
9–10 yrs.	320	158	49.4	113	74	65.4	433	232	53.6
10–11 yrs.	330	164	49.7	93	53	57.0	423	217	51.3
11–12 yrs.	308	159	51.6	117	79	67.5	425	238	56.0
12–13 yrs.	274	153	55.8	100	70	70.0	374	223	59.6
13–14 yrs.	274	175	63.9	99	70	70.7	373	245	65.7
14–15 yrs.	198	139	70.2	95	60	63.2	293	199	67.9
0– 1 yr.	66	12	18.2	78	14	17.9	144	26	18.1
0– 5 yrs.	785	316	40.3	533	187	35.1	1,318	503	38.2
5–10 yrs.	1,552	662	42.7	645	358	55.5	2,197	1,020	46.4
10–15 yrs.	1,384	790	57.1	504	332	65.9	1,888	1,122	59.4
0–15 yrs.	3,721	1,768	47.5	1,682	877	52.1	5,403	2,645	49.0

According to color (data available for 5,403 children) the frequency of positive reactions among the white children, 48 per cent, differed little from the 52 per cent of the colored.

Contact with other cases raised as usual the proportion of those infected, especially among the young. Of all children under five years of age with a history of contact, 41 per cent reacted, as against 28 per cent when no such history was noted. Among those five to ten years old,

there was also an excess of reactors among the contact children: 53 per cent positive compared with 26 per cent among those without known history of contact; and among those ten to fifteen years, 64 per cent

TABLE 7

Intracutaneous tuberculin tests upon 6,429 children, according to "history of contact," among those admitted to eight tuberculosis clinics, New York City, 1930–1932

AGE	POSITIVE HISTORY OF CONTACT			NEGATIVE HISTORY OF CONTACT			TOTAL		
	Tested	Reacted		Tested	Reacted		Tested	Reacted	
		Number	Per cent		Number	Per cent		Number	Per cent
0– 3 mos.	23	3	13.0	2	1	50.0	25	4	16.0
3– 6 mos.	45	7	15.6	3	1	33.3	48	8	16.7
6–12 mos.	73	16	21.9	15	2	13.3	88	18	20.4
1– 2 yrs.	175	60	34.3	25	6	24.0	200	66	33.0
2– 3 yrs.	276	117	42.4	47	10	21.3	323	127	39.3
3– 4 yrs.	328	139	42.4	63	18	28.6	391	157	40.2
4– 5 yrs.	362	179	49.4	85	28	32.9	447	207	46.3
5– 6 yrs.	360	184	51.1	116	28	24.1	476	212	44.5
6– 7 yrs.	394	187	47.4	153	40	26.1	547	227	41.5
7– 8 yrs.	400	201	50.3	134	31	23.1	534	232	43.4
8– 9 yrs.	380	212	55.8	171	47	27.5	551	259	47.0
9–10 yrs.	391	227	58.1	119	37	31.1	510	264	51.8
10–11 yrs.	383	215	56.1	131	44	33.6	514	259	50.4
11–12 yrs.	388	243	62.6	137	54	39.4	525	297	56.6
12–13 yrs.	354	227	64.1	116	48	41.4	470	275	58.5
13–14 yrs.	331	228	68.9	108	55	50.9	439	283	64.4
14–15 yrs.	255	177	69.4	86	51	59.3	341	228	66.9
0– 1 yr.	141	26	18.4	20	4	20.0	161	30	18.6
0– 5 yrs.	1,282	521	40.6	240	66	27.5	1,522	587	38.6
5–10 yrs.	1,925	1,011	52.5	693	183	26.4	2,618	1,194	45.6
10–15 yrs.	1,711	1,090	63.7	578	252	43.6	2,289	1,342	58.6
0–15 yrs.	4,918	2,622	53.3	1,511	501	33.2	6,429	3,123	48.6

reactors in the first group, and 44 per cent in the second. Altogether, of clinic children under fifteen years of age, contacts averaged 53 per cent reactors and noncontacts 33 per cent.

As to the clinical significance of these infections certain figures are available in New York City for just these particular tuberculosis-clinic children. During 1929 and 1930, of 7,927 such contact children examined, only 102 or 1.3 per cent were found to have clinical or manifest disease. Other reports of contact children examined also available to the

writer disclose practically the same results, namely, of 5,597 children examined at the dispensaries of the Chicago Municipal Sanitarium, during 1927 and 1928, 74 showed clinical tuberculosis; and therefore, here too, only 1.3 per cent. Again in London, where nonpulmonary forms of tuberculosis are more frequent than in American cities, reports of the Medical Officer of the County Council for the three-year period 1927–1929, show, of 14,628 examined at the various clinics of the 27 metropolitan boroughs (and the cities of Westminster and London) that there were 284, or 1.9 per cent, with clinical tuberculosis. Obviously, under present conditions, the very great majority of children infected with the tubercle bacillus do not develop active disease.

An illuminating and recent observation of the small number of children who, though infected with tuberculosis, develop actual disease is at hand from the Brompton Hospital in London. There, Lloyd and Macpherson (5) reported on their observations after retesting and reëxamining 700 children "after an interval of one and a half years to two years, with a view to finding whether there was any change in reaction to the tuberculin tests, and whether any of them had developed clinical signs and symptoms of tuberculosis." Of 303 who were positive reactors when first tested, 12, or 4 per cent, became negative; of the other 397, negative at first, 343 remained so, and 54, or 14 per cent, had in the interval become infected and showed positive reactions now; altogether, therefore, 345, or nearly half of the 700 retested, were now positive. Further, in the entire group of 700, originally "seven," or one per cent, "were suffering from pulmonary tuberculosis . . . . but when seen at the time of the second test they had all improved and the disease was quiescent. . . . . Of the other 693, none has developed clinical tuberculosis during the interval between the two tests." Besides, included therein were 24 children "reactors under five years of age,[8] fourteen of which were contacts;" not one of these "had had an acute dissemination of the disease," and none, except perhaps one "had slightly enlarged discrete cervical glands, which had remained unaltered since 1930."

INFECTION IN OTHER CITIES

It has been interesting to compare the recent findings of tuberculous infection in New York with those of other large cities; since, after all, it is in the great and congested centres of population that we should expect

[8] Two of which were under two years.

the largest amount of, or, at least, the most frequent opportunities for infection. For instance, surveys, all based on the intracutaneous test, are available for Chicago, made during 1930–1931 by Webb; for Philadelphia during 1926 by Hetherington *et al.*; for Minneapolis in 1926, by Harrington and Myers; for San Francisco during 1925 to 1928, by Dickey and Seitz; for Detroit in 1929, by Johnston and Chadwick; and, for London in 1930–1931, by Dow and Lloyd. The results are shown in table 8.

In New York City, the data compared are drawn from the combined figures of all the tests: first, upon the 6,080 children in the three general hospitals, and, second, upon the 1,965 children in the seven special clinics, baby health-stations, preschool and other "well" clinics, previously mentioned, but exclusive of those in the tuberculosis clinics; altogether, therefore, the results among 8,045 children tested during the three years 1930, 1931 and 1932. The findings, summarized, show here only 4 per cent of infants under one year reacting; 9 per cent of all under five years; 18 per cent of those five to ten; 31 per cent of those ten to fifteen; and, an average for all under fifteen years of age of only 14 per cent, though it may be recalled the children included are mostly from the poor and from the thickly populated Borough of Manhattan. Perhaps it might not be amiss to add that in 1931, for instance, the tuberculosis death-rate in New York City was down to 69 per 100,000 and nearly 20 per cent lower than it was in 1926; also, that during the "economic depression," there has been a very large increase in the number of those hospitalized or going to public sanatoria. However, for the period 1921–1928 Smith (6) had already shown that the percentage of infection in the children admitted to Bellevue Hospital had, each year, averaged 16 per cent.

In Chicago, Webb (7) recently reported findings among 1,000 children tested with 1 mgm. of synthetic-medium tuberculin prepared by Dr. Seibert, during the year 1930–1931 by the staff-members of the Pediatrics Out-Patient Department of the University of Chicago Clinics. "The Clinic material," says Webb, "was drawn from the middle-class population." Also, 87 of the children were "contacts" and they furnished 40 of the 145 positive reactions. In this Chicago series, 3.5 per cent of the infants reacted positively; only 7.6 per cent of all under five years; 14 per cent of those five to ten years old; 22 per cent, of those ten to fifteen; and an average for the entire group under fifteen of 14.5 per cent,—practically the same as the New York City average.

TABLE 8

Percentage of children under fifteen reacting to intracutaneous tuberculin tests from surveys in seven great cities

	NEW YORK CITY 1930–1932	CHICAGO, ILLINOIS 1930–1931	PHILADELPHIA 1926	DETROIT, MICHIGAN 1929	MINNEAPOLIS 1926	SAN FRANCISCO 1925–1928	LONDON, ENGLAND 1930–1931
Children.....	8,045	1,000	2,678	2,467	2,045	3,500	1,003
Authors.....	(G. J. D.)	(7)	(8)	(9)	(10)	(2)	(12)
Age:							
0– 1 yr.	4.4	3.5		1.7			
1– 2 yrs.	8.2	7.9		7.5		5.6	0
2– 3 yrs.	10.6	5.8		4.0		13.6	12.9
3– 4 yrs.	12.8	9.0	40.0	7.0		16.9	30.8
4– 5 yrs.	16.0	8.8	42.1	14.3		19.8	24.6
5– 6 yrs.	14.5	13.0	37.7	13.3		20.6	24.4
6– 7 yrs.	14.1	10.0	43.1	12.6	20.8	16.5	44.3
7– 8 yrs.	17.3	10.7	47.7	16.0	27.4	16.1	40.6
8– 9 yrs.	23.1	14.4	62.2	17.0	38.9	26.4	42.0
9–10 yrs.	23.7	23.6	63.5	18.1	41.1	27.7	46.2
10–11 yrs.	30.4	23.6	70.9	22.4	50.6	26.2	47.3
11–12 yrs.	31.1	22.6	73.1	15.3	50.0	38.0	54.4
12–13 yrs.	29.2	16.1	77.6	16.7	59.7	39.1	66.7
13–14 yrs.	44.1	21.1	77.9	28.3	58.4	42.2	55.0
14–15 yrs.	42.1	30.5	79.9	16.7	69.5	46.6	82.2
0– 5 yrs.	9.2	7.6	41.7*	6.9		15.1‡	23.0‡
5–10 yrs.	18.1	14.0	54.2	15.5	34.9†	20.9	39.0
10–15 yrs.	31.4	22.3	76.6	19.2	56.8	36.9	58.3
0–15 cru.§	13.6	14.5	68.5*	14.1	47.3†	23.5‡	43.1‡
0–15 adj.§	19.2	14.4	61.0*	13.6	46.8†	24.6‡	40.8‡

* Beginning with those 3 years old only.

† From 6 years on.

‡ From one year on.

§ Crude percentage for the entire group in each city, where obviously different proportions of children of various ages were tested. Adjusted, by applying the specific ratios of each age group to a common, comparable child-population, namely, that of the children in the standard million of England and Wales for 1901: under five, 114,212; five to ten, 107,209; ten to fifteen, 102,735. Thus in New York City, the percentage found reacting would indicate 62,176 infected in the total under fifteen of 324,206 children in the standard million—or 19.2 per cent positive. In Philadelphia, 155,478 infected among 254,730 aged three to fifteen —61.0 per cent. Similarly, for Minneapolis figures of only the children aged six to fifteen in the standard million, as in the group tested, were utilized; for San Francisco and London, the fraction under one year was excluded.

Webb underestimates, we think, the significance of these low percentages, stating it was "far below the incidence found in crowded tenement districts," for which he gives no figures. The writer (Drolet) is familiar with the unusually well coördinated public-control machinery for tuberculosis existing in Chicago, through home sanitary supervision, well-located dispensaries, and highly organized sanatorium facilities, all unified under the single management of the Chicago Municipal Sanitarium. Also in Chicago, a drastic sanitary requirement has been that children in contact with open cases of tuberculosis, whether rich or poor, must be separated from the endangering parent, relative or other source, this being usually accomplished by the patient going to an institution or "taking the cure" elsewhere. As a result, Chicago for several years has had, even though it has a goodly-sized colored population and there has been an influx at times of Mexican laborers, the lowest tuberculosis death-rate of any great city. We believe that this more thorough supervision, care, and follow-up of original cases has played a material part in producing the marvelously low proportions of children infected in Chicago which Webb has revealed. We know that elsewhere a marked correlation has been found between the number of cases hospitalized and the deaths from tuberculous meningitis among children; when the first increases the latter decreases, and *vice versa* when fewer are segregated in institutions.

For Philadelphia, there is the thorough survey of certain schoolchildren, 2,678 aged three to fifteen, reported upon by Opie (8) and his colleagues. These children, however, were tested in 1926; and among them it must be noted that more than a third (37 per cent) were colored; also, that there was careful retesting with higher dosages of tuberculin up to 1.0 mgm. of those failing to react to smaller doses; finally that they were drawn from poorer districts. Among the children three to five, 42 per cent reacted; among those five to ten years, 54 per cent; among those ten to fifteen, 77 per cent; and, an average, for the entire group, three to fifteen years, of 68.5 per cent,—very high figures for a child population. As a matter of fact, these figures exceed in every age-group the proportions found infected in New York City even among the children with a "positive history of contact" seen in the tuberculosis clinics here,—more recently though, it should be admitted, if time and lower death-rates have a bearing.

From Detroit, there has come to hand recently the preliminary report of Johnston and Chadwick (9) of tests on 2,467 children, under fifteen

years of age, in that large industrial centre. One-tenth of one milligram of Old Tuberculin, intracutaneously, was used,—as the authors add, "sufficiently strong to detect all but a few reactors." The children, tested in 1929, were "routinely examined on their admission to a foster-home agency (The St. Vincent de Paul Society); they were all white; the economic status was low." Furthermore, it is stated that there was "a history of exposure to human cases in 55 per cent." Johnston and Chadwick also remark that "less than 0.5 per cent of the cows in Michigan react to the tuberculin test, and over 99 per cent of the milk sold in Detroit was pasteurized." They might also have added that facilities for hospitalization and segregation of tuberculosis cases in that city have been unusually ample,—twice as many beds available as the annual number of deaths.

In Detroit, as in the recent survey in Chicago and New York City, an average of only 14 per cent of the children under fifteen reacted; of those from birth to five, 6.9 per cent; of those five to ten, 15.5 per cent; and, of those ten to fifteen, 19.2 per cent.

In Minneapolis, Harrington and Myers (10), using successive doses of 1:1000 and 1:100 of diluted tuberculin, have reported their findings among 2,045 school children, six to fifteen years old, tested during 1926. Among those six to ten years, 35 per cent reacted positively; among those ten to fifteen, 57 per cent; and, for the entire group six to fifteen years old, an average of 47 per cent.

On the Western Coast of the United States, we have for San Francisco the surveys of Dickey and Seitz (2), using "standard 0.1 mgm. of tuberculin," from 1925 to 1928 among 3,500 children "unselected and tested regardless of complaint as they registered in the Children's Clinic of the Stanford University Medical School." The authors also add that "the dispensary is a part-pay clinic which admits some indigent patients and none are well-to-do." It is further stated in a preliminary report that 23 per cent of the children had "a definite history of exposure to tuberculosis,"—a proportion much greater than in a normal population. Among children from at least a year old to five years, 15 per cent reacted positively; among those five to ten, 21 per cent; among those ten to fifteen, 37 per cent; and an average, for the entire group, of only 23.5 per cent, much more in consonance with the low proportions in Chicago or New York, but little over a third of those reported in Philadelphia. That these low percentages in the Stanford Clinic group of children are probably not an underestimate of that type of population there is sup-

ported by the other findings of Dickey (11) that even among children of Chinese and Japanese residents in San Francisco, who suffer a tuberculosis mortality rate four times that of the rest of the city, they found only 35 per cent reacting in a group of 119 two to fourteen years old.

Finally, for London, there is the report of Dow and Lloyd (12) at the Brompton Hospital for Consumption and Diseases of the Chest, for 1,003 children tested in 1930 and 1931, to whom they gave successive injections, when the first remained negative, of 0.01, 0.1, and 1 mgm., as was done in Philadelphia. Those children, the authors state, were "for the most part from families of an urban working-class population." Furthermore, it is indicated that 28 per cent were "contacts." Even so, the entire group averaged, for children from one year old to fifteen, 43 per cent: of those under five, 23 per cent; those five to ten years old 39 per cent; and, of those ten to fifteen, 58 per cent. The reader should also be reminded that in England nonpulmonary forms of tuberculosis prevail far more than in the United States; and that recent reports of the Medical Officer of the London County Council still show that tubercle bacilli are found in 8 to 10 per cent of milk-samples taken there.

CHANGES IN BELLEVUE HOSPITAL CHILDREN

Smith (6) having already published the results of intracutaneous tests upon patients in the Children's Medical Division of Bellevue Hospital during the eight-year period, 1921–1928, we have compared the proportions of those reacting more recently, namely, the children in the same wards during the years 1930 and 1931, to see what changes, if any, have taken place in the percentages of those found infected. No significant differences were found, even though it is reported that of late a number of Porto Rican and colored children are now being admitted, whereas formerly those of foreign extraction were mostly of Irish or Italian parentage.

Among 7,668 children under thirteen years of age tested between 1921 and the end of 1928, 1,286, or 16.9 per cent, reacted; among 3,720 of the same age, during the two years 1930 and 1931, 595, or 16.0 per cent, were reactors. Only some slight variations, probably not significant, were noted when smaller age-groups were considered. During the earlier eight-year period, of the babies under one year of age 5.3 per cent reacted; during the second and more recent period, 3.8 per cent were positive. Among all those under five years of age, 9.9 per cent reacted formerly against 10.6 per cent recently; among those five to ten years,

26.1 per cent compared with 24.1 per cent; and, among those ten to thirteen years, 39.4 per cent reactors, as against 35.4 per cent lately.

What Smith described formerly at Bellevue Hospital continues to hold today: "We have found," he said, "about 16 per cent Mantoux reactions each year, and the curves," according to age, "are almost identical in each year."

As against this uniformity, however, an important general remark must be made. Bellevue Hospital, a large municipal institution, serves mostly residents of the Borough of Manhattan. Kings County Hospital and Fordham Hospital serve those of the boroughs of Brooklyn and the Bronx, respectively. And, whereas tuberculosis mortality in the last two sections has fallen markedly during the past decade, it is notorious that in the older, central and practically all built-up borough of Manhattan, tuberculosis has remained rampant and uncontrolled. In 1921 the tuberculosis death-rate of Manhattan was 130 per 100,000 population and in 1931 was still 127, whereas in Brooklyn it had fallen, for the same years, from 87 to 51, or by 41 per cent, and in the Bronx from 82 to 48, or again by 41 per cent.

During 1921 the registration-rate for new cases of tuberculosis in Manhattan was 331 per 100,000 population, and in 1931 it was still 324, while in the other four boroughs, during the last-mentioned year, it only ranged between 99 in Queens and 135 in Brooklyn. Let us recall too that Manhattan harbors not only its own residential population of nearly two million, but another three million, who rush in during the day from the other boroughs or the metropolitan area for work, business, shopping or visiting. The wonder perhaps, with this constantly rising tide, is not that only 16 per cent of the children under thirteen years of age among those living here, going to school and trying to play in these congested streets, are infected, but that the proportion has not mounted higher. More significant perhaps than a common level of infection among children in the hospital wards of Bellevue during the past decade are the changes among children tested in the tuberculosis clinic of Bellevue Hospital recently and twenty years ago. "Contact" children tested there (13) only by "cutaneous application" during the years 1912 to 1916 showed, among those from infancy to fifteen years of age, an average of 64 per cent reactors. A similar group, tested this time intracutaneously during the period 1930–1932, showed among contacts of the same age, 46 per cent.

FATALITY RATE AMONG INFECTED CHILDREN

If the findings with the intracutaneous tests in the childhood clientele of the various hospitals and clinics surveyed in New York City be really representative of the incidence of tuberculous infection, it is readily

TABLE 9A

*Number of deaths from tuberculosis among children in New York City, three-year period, 1930–1932**

AGE	WHITE		COLORED		TOTAL	
	Male	Female	Male	Female	Three years	Annually
0– 3 mos.	7	3	2	1	13	4
3– 6 mos.	18	5	2	1	26	9
6–12 mos.	66	44	23	14	147	49
1– 2 yrs.	70	64	26	29	189	63
2– 3 yrs.	59	45	24	24	152	51
3– 4 yrs.	36	34	12	18	100	33
4– 5 yrs.	14	14	23	11	62	21
5– 6 yrs.	15	5	10	7	37	12
6– 7 yrs.	21	11	7	5	44	15
7– 8 yrs.	13	11	3	3	30	10
8– 9 yrs.	6	7	9	6	28	9
9–10 yrs.	7	12	7	8	34	12
10–11 yrs.	11	4	7	5	27	9
11–12 yrs.	10	14	7	6	37	12
12–13 yrs.	8	10	5	9	32	11
13–14 yrs.	12	18	5	14	49	16
14–15 yrs.	10	29	6	9	54	18
0– 1 yr.	91	52	27	16	186	62
0– 5 yrs.	270	209	112	98	689	230
5–10 yrs.	62	46	36	29	173	58
10–15 yrs.	51	75	30	43	199	66
0–15 yrs.	383	330	178	170	1,061	354

* From data by courtesy of Dr. John T. Walsh, Bureau of Records, Department of Health.

possible from the mortality records of the same years to ascertain the present fatality rate[9] among children infected.

For instance, the Department of Health of the City of New York

[9] The term is used here in the same sense as defined by Hart (14), namely, that "The fatality-rate of tuberculous infection in a community is . . . . the ratio between the annual number of deaths from tuberculosis and the mid-year population expressed in hundreds."

reports that during the three years 1930, 1931 and 1932, tuberculosis deaths among infants averaged 62 annually; among all children under five years, 230; among those five to ten, 58; and, among those ten to fifteen, 66.

Second, the annual total deaths, from the same cause, at all ages, namely, for children and adults, during the same years, numbered 4,850, or roughly five thousand.

Third, according to the studies of the American Public Health Association, there are on an average five living cases on a given date to each death annually, which would indicate 25,000 living cases in New York City: actually the known cases or the total registered on December 31,

TABLE 9B

Annual death rate from tuberculosis among children, New York City, three-year period, 1930–1932*

AGE	WHITE		COLORED		BOTH RACES	RATIO COLORED TO WHITE	
	Male	Female	Male	Female		Male	Female
0– 1 yr.	63	38	351	212	63	6:1	6:1
0– 5 yrs.	35	28	259	226	43	7:1	8:1
5–10 yrs.	7	6	90	70	10	13:1	12:1
10–15 yrs.	6	9	100	140	11	17:1	16:1
0–15 yrs.	16	14	158	147	21	10:1	10:1

* Per 100,000 living in each group.

1931, numbered 19,158. Experience, however, shows that of those registered only a portion have positive sputum or are "open cases,"—the ones spreading infection. But, not to underestimate, 25,000, as first figured, might be accepted a fair statement of all possible sources of infection.

Fourth, allowing an average of two children in "home contact" per case, it can be estimated that the total child-population of that type may reach 50,000.

Fifth, in New York City, the midyear population for 1931 under fifteen years of age was figured at nearly 1,700,000 (see table 10).

Taking these points and facts under consideration, and applying the percentages of reactions from the recent surveys, first, in the comparatively normal child-population and, second, among contacts, we find,

TABLE 10

*Child-population, New York City**

AGE	WHITE			COLORED			GRAND TOTAL
	Male	Female	Total	Male	Female	Total	
0– 1 yr.	47,905	45,942	93,847	2,565	2,499	5,064	98,911
0– 5 yrs.	256,057	246,812	502,869	14,422	14,486	28,908	531,777
5–10 yrs.	281,021	273,975	554,996	13,372	13,841	27,113	582,109
10–15 yrs.	285,405	279,340	564,747	9,952	10,244	20,196	584,943
0–15 yrs.	822,485	800,127	1,622,612	37,646	38,571	76,217	1,698,829

* As of July 1, 1931; annual increase averages nearly ten thousand (9,362).

TABLE 11

Fatality-rate from tuberculous infection among children in New York City (based upon data for three-year period, 1930–1932)

AGE	CHILD-POPULATION, LESS CONTACTS	INFECTED		"CONTACT" CHILDREN			TOTAL INFECTED	ANNUAL	
		Per cent	Number	Total number	Infected			Tuberculosis deaths	Rate per 100 infected
					Per cent	Number			
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
0– 1 yr.	95,911	4.4	4,220	3,000	18.4	552	4,772	62	1.30
0– 5 yrs.	516,777	9.2	47,543	15,000	40.6	6,090	53,633	230	0.43
5–10 yrs.	565,109	18.1	102,285	17,000	52.5	8,925	111,210	58	0.052
10–15 yrs.	566,943	31.4	178,020	18,000	63.7	11,466	189,486	66	0.035
0–15 yrs.	1,648,829	19.9	327,848	50,000	53.0	26,481	354,329	354	0.099

Notes: (1) As of July 1, 1931; see table 10.
(2) Based on survey in three general hospitals and seven special clinics; see tables 1, 4 and 8.
(3) Obtained by applying ratios reacting to population in (1); total is from sum of the parts and the percentage for the entire group, 0–15, is derived therefrom.
(4) Based upon actual registration of tuberculosis deaths and cases; see text also.
(5) From survey in eight tuberculosis district clinics; see table 7.
(7) Sum of (3) and (6).
(8) Annual average; see table 9A.
(9) For infants 1.3 deaths annually per 100 infected, or, 1,297 per 100,000; similarly for all under five 0.43 deaths per 100 infected or 430 per 100,000, etc.

as indicated in table 11, that among infants under one year totalling 98,911 with the number infected reaching nearly five thousand (4,772) and, the deaths numbering 62, the fatality rate was only 1.3 per each

hundred children infected; or 1,297 per 100,000,—a higher mortality rate, however, than that usually quoted from, or based upon, the total infant population, infected and uninfected, but in no wise supporting statements which have been made of the extreme seriousness of such infection among infants.

Similarly, among the 531,777 children under five years of age, with the number infected at 53,633 and 230 deaths, the fatality rate, it is seen, figures 0.43 per hundred infected; or, 430 per 100,000 of that age, instead of the 43 per 100,000 for the year 1931 based upon the total population infected and uninfected in that group.

Among children five to ten years of age, numbering in New York City nearly six hundred thousand (582,109), with the number infected figuring 111,210 and only 58 deaths, the fatality rate was 0.052 per hundred infected; or, 52 per 100,000.

Finally, among children ten to fifteen, numbering here 584,943, with 189,486 infected and 66 deaths, the fatality rate was 0.035 per hundred infected; or, 35 per 100,000.

Should the recent surveys in New York City have underestimated the present prevalence of infection, all that one might conclude then is that the fatality rates would be still lower than those just stated.

Obviously, under general conditions such as exist here, only a very small fraction of children infected with tuberculosis succumb to it—even among infants. That contrary opinions have been common in the past, especially regarding the very young, may be partly explained if we recall the very much higher mortality rates of but a few years ago (see figure 1). In 1898, as previously pointed out (15), the infant death-rate for tuberculosis was 609 per 100,000 children under one year of age, whereas in 1932 it was only 44 per 100,000 births (practically the same unit of comparison) a reduction of nearly 93 per cent. At that time, such a thing as "early diagnosis" of a diseased father or mother was only accidental if made at all; there was no pasteurization of infected milk; home sanitary supervision and instruction by visiting nurses as to the danger of spreading infection never took place; very few could go to a sanatorium or tuberculosis hospital (few institutions existed for that matter); and segregation, forcible removal of careless patients, was not even considered. Imagine, in crowded old-law tenements, many with windowless rooms, the repeated dosage of infection children remained exposed to when in contact with a tuberculous parent or relative. The impressions of some as to mortality rates among young children from

tuberculous infection have, we fear, often been gathered from those exposed to conditions as just described, which of course simply don't exist here now.

From data gathered, somewhat midway between 1898 and 1932, namely, on the results of tuberculin tests made during the five-year period,

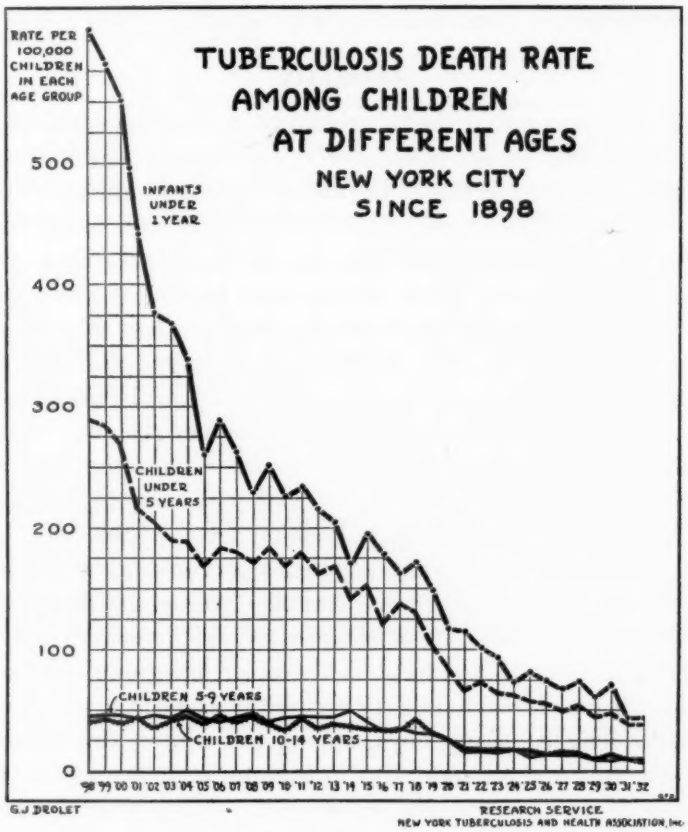
TUBERCULOSIS DEATH RATE
AMONG CHILDREN
AT DIFFERENT AGES
NEW YORK CITY
SINCE 1898
RATE PER 100,000 CHILDREN IN EACH AGE GROUP
500
400
300
200
100
0
INFANTS UNDER 1 YEAR
CHILDREN UNDER 5 YEARS
CHILDREN 5-9 YEARS
CHILDREN 10-14 YEARS
'98 '99 '00 '01 '02 '03 '04 '05 '06 '07 '08 '09 '10 '11 '12 '13 '14 '15 '16 '17 '18 '19 '20 '21 '22 '23 '24 '25 '26 '27 '28 '29 '30 '31 '32
G.J. DROLET
RESEARCH SERVICE
NEW YORK TUBERCULOSIS AND HEALTH ASSOCIATION, Inc.

FIG. 1

1912 to 1916, an idea may be gathered of conditions then and of changes in the prevalence of infection. The writer (13) found that children from the East Side attending the tuberculosis clinic of Bellevue Hospital, then tested only *cutaneously* (Pirquet method), showed, among "contacts," 69 per cent of positive reactors among those five to ten years old, and 75 per cent among those ten to fifteen. In the recent survey, for 1930–1932, at the same clinic, among contact children from the same

neighborhood, but tested this time *intracutaneously*, those five to ten years old gave 43 per cent of positive reactions; and, those ten to fifteen only 54 per cent. But in 1914, in New York City, the general tuberculosis death-rate was still 200 per 100,000 population, whereas in 1931 it was 69 or reduced by two-thirds; also, the total of old and new known cases actually in the tuberculosis register of the Department of Health during the entire year 1914 footed 54,043,[10] whereas in 1931 it was 31,621.

MORTALITY

For the same years that the tuberculin tests were made, namely, 1930, 1931 and 1932, the Bureau of Records of the Department of Health has kindly made available figures of the number of deaths among all children in New York from tuberculosis classified by single years of life and separately for the white and colored boys and girls (see part A, table 9).

In a child-population, under fifteen years of age, of more than one million and a half (1,698,829), of which 76,217, or less than 5 per cent, were colored, a total of 1,061 deaths were registered during the three-year period 1930–1932; an average annually of 354, and a death-rate of 21 per 100,000. Among infants, the rate was 63 per 100,000. Among all under five, 43; those five to ten, only 10; and in those ten to fifteen, 11.

Of the total, 1,061 deaths, 444, or 42 per cent, were of the meningeal type; 355, or 33 per cent, of the pulmonary form; 41, or 4 per cent, intestinal; and 221, or 21 per cent, of other forms of tuberculosis (see also figure 2). Though only comprising but one-twentieth of the population, colored children suffered 348, or one-third of all the deaths. By sex, it seems in both races that, except in the older age-group, ten to fifteen years old, when girls reach puberty earlier than boys, the male mortality exceeds the female. Baby boys, among the whites, furnished 64 per cent of the tuberculosis mortality in infants; and, among the colored, practically the same proportion, 63 per cent. Since, generally speaking, namely, in New York City and other communities, positive tuberculin reactions show almost equal proportions of infected children of either sex or color, it is impossible to explain on the mere score of infection the different mortality rate at certain ages of boys from that of girls, or of colored children from that of white which manifests itself from the very start of life; other conditions, constitutional mostly, must be recognized.

[10] Made up of 29,439 known cases in the register on January 1, 1914, of 21,604 new cases reported during the year, and of 3,000 "old cases resumed." In 1931 the year started with 18,866 known cases, to which were added during the year 11,794 new cases and 961 resumed old cases.

As noted in the chapter on the fatality rate from tuberculous infection, and in table 9B of specific mortality rates, the customary differences appear again in the New York data: the largest number of deaths occur in infancy; after the third year of life, these begin to drop rapidly. School-boys until they are sixteen or seventeen, and school-girls, until they are fourteen or fifteen, enjoy a golden period comparatively free from tuberculosis mortality.

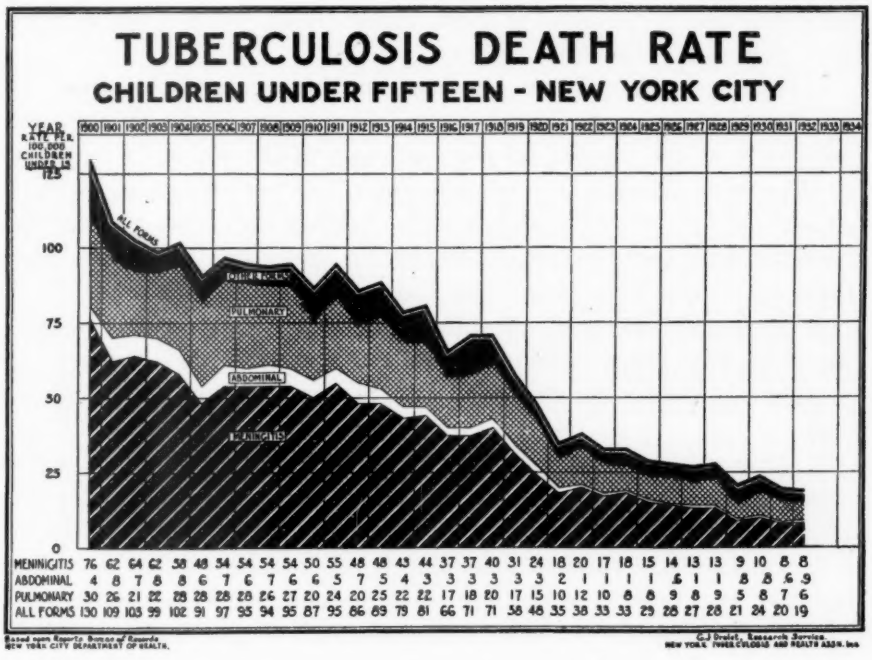

FIG. 2

The excessive mortality rates of colored children in comparison with those of the white, though reported previously, for instance by Whitney (16) and Sydenstricker (17) for certain states, and by Weiner (18) for New York City, must be noted again during those three years for which records of infection are available (see table 9B). Among all the colored children under fifteen years, the tuberculosis death-rate during the three-year period, 1930–1932, was ten times that of the white children, namely, colored boys 158 and white boys 16, colored girls 147 and white girls 14. Within smaller age-groups, differences were even greater:

while among infants the colored death-rate was six times that of the white, among colored girls ten to fifteen it was 16 times that of white girls and in colored boys 17 times that of white boys.

SUMMARY

1. To ascertain the present incidence of tuberculous infection among children in New York City, the records of tuberculin tests, given intracutaneously only, during the years 1930, 1931 and 1932, were assembled for nearly fifteen thousand of those under fifteen years of age in three general hospitals and fifteen clinics.

2. Among 6,080 children admitted to three general hospitals, an average of 13 per cent of the boys and 15 per cent of the girls reacted positively; of the colored, 15 per cent, and, of the white, 11 per cent; of those with a history of "home contact," 35 per cent, and, of those with a negative history, 10 per cent. Infants under one year of age furnished 4 per cent of reactors; all children under five years, 9 per cent; those five to ten years, 19 per cent; those ten to fifteen, 29 per cent.

3. Seasonally, no significant differences in the percentages of positive reactions were noted: during November, December and January, an average of 12 per cent; during August, September and October, 14 per cent.

4. Among 1,965 children attending seven "well" baby, preschool or other clinics, 13 per cent reacted positively; 9 per cent of those under five; 16 per cent of those five to ten; and 40 per cent of those ten to fifteen.

5. Among 6,429 children attending 8 tuberculosis clinics in various parts of New York City, positive reactions averaged 49 per cent: boys, 47 per cent; girls, 50 per cent; white children, 48 per cent; colored, 52 per cent; positive history of home contact, 53 per cent; negative history of contact, 33 per cent. By age, among those under one, 19 per cent positive; all under five years, 39 per cent; those five to ten, 46 per cent; and, those ten to fifteen, 59 per cent. By residence, no significant differences according to boroughs, but in Brownsville, where the tuberculosis death-rate is lowest in the city, positive reactions were lowest, namely, 33 per cent.

6. Recent surveys in other cities with intracutaneous tests show, against New York City's average (in the hospitals and special clinics) of 14 per cent positive reactions, in Chicago, 15 per cent; in Philadelphia, 69 per cent; 14 per cent in Detroit; in Minneapolis, 47 per cent; in San Francisco, 24 per cent; and, in London, 43 per cent. But, adjusted,

comparable rates, based upon a standard child-population, comprising all under fifteen years of age, would show in New York City 19 per cent reacting; in Chicago, 14 per cent; in Detroit, 14 per cent; for the group one-year-old to fifteen in San Francisco, 25 per cent; and, in London, 41 per cent; for the age-group six to fifteen, in Minneapolis, 47 per cent; and for those three to fifteen in Philadelphia, 61 per cent.

7. The annual fatality rate from tuberculous infection in New York City during the period 1930–1932 is figured among infants at 1.3 per each 100 infected, or 1,297 for 100,000; among all under five, 430 per 100,000; those five to ten, at 52 per 100,000; among those ten to fifteen, at 35 per 100,000 infected: and, for the entire group, at less than one-tenth of one per cent.

8. An annual average of 354 deaths from tuberculosis among all children under fifteen occurred in New York City during the three-year period 1930–1932, a mortality rate of 21 per 100,000. One-third of the deaths was of colored children, though that group is but one-twentieth of the child-population, which totals 1,700,000 in New York City. The death-rate of the colored children, 152 per 100,000, was ten times that of the white children, which was only 15. Among young children, the male mortality exceeds the female; and, even with infection less frequent in early childhood than later, the highest death rates occur then. Along with infection, constitutional factors of sex and color must also be taken into consideration to account for obvious differences from the start of life in the implantation and progress of tuberculosis.

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THE LYMPHATIC REACTION IN TUBERCULOSIS[1,2]

BRUCE K. WISEMAN AND CHARLES A. DOAN

The finer analysis of the cellular changes induced in the tissues by the tubercle bacillus forms a brilliant chapter in the more recent history of our developing knowledge of tuberculosis. Of scarcely less interest and of parallel importance are those studies in which an attempt has been made to correlate the observed changes in the histopathology of the tissues with qualitative and quantitative changes in the cytological constituents of the peripheral blood. Thus, the fundamental investigations of Sabin, Cunningham, Doan and associates (1) (2) (3) (4) have demonstrated that actively spreading tuberculous lesions are reflected in the blood by an absolute increase of monocytes, the monocyte having first been proved by these same investigators (5) to be the *Anlage* of the epithelioid cell, an essential constituent of the tubercle. Similarly, Shilling (6) and Bredeck (7) have shown that the effect of tuberculous toxaemia on the bone-marrow may be measured by the qualitative variations in the granular leucocytes, and Medlar (8) has added the concept that a sustained high numerical level of neutrophilic granulocytes in the blood may indicate localized mobilization of these elements in the tissues at the point of tuberculous invasion or dissemination, and frequently presages the advent of suppuration, caseation and cavity-formation.

Earlier, however, than any recognition of the above-described cell changes, were the observations suggesting the existence of a relationship between the lymphocyte and tuberculous disease. Arloing in 1882 (9) was one of the first to point out that lymphocytes may be important reacting units in tuberculosis. Subsequent early observations (10) (11) (12) (13) (14) (15) (16) (17) *et al.*, as well as a vast number of later publications have repeatedly called attention to the high level of lymphocytes found in the blood, when healing of the tissue lesions and resistance to

[1] From the Department of Medical and Surgical Research, Ohio State University, Columbus, Ohio.

[2] Presented in part before the Pathological Section at the twenty-ninth annual meeting of the National Tuberculosis Association, Toronto, Ontario, under the title *Progressive Qualitative Changes in the Lymphocytes of the Blood in Pulmonary Tuberculosis*, June 30, 1933.

the spread of the disease are apparent. More recently this concept has been modified and amplified through a recognition of the importance of the ratio of monocyte to lymphocyte in the blood of tuberculous individuals (18) (19) (20) (21) (22) (23) (24) (25) (26) (27). This general basis for prognosis, however, established upon a consideration of numerical factors has failed not infrequently of prognostic reliability. Two explanations may be suggested in accounting for the exceptions noted: (1) Many of the blood studies recorded in the literature were made before a full realization of the importance of sharply differentiating monocyte and lymphocyte had become as apparent as it is to-day, with the result that a variable number of the monocytes have been and continue to be classified in many laboratories under the general heading of "lymphocytes"; and (2) even with adequate differentiation of the mononuclear cells, there have been no criteria hitherto available comparable to that which exists in the Arneth-Shilling index for granulocytes, by which the real extent of the lymphatic reaction could be judged.

The demonstrated value of determining the reactive capacities of the bone-marrow and connective tissues by a study of the qualitative variations in the blood of the granular and monocytic cells, respectively, suggested the desirability of determining similar data with respect to the lymphatic tissues and the lymphocytes. Certain findings and interpretations by one of us (B. K. W.) in a preliminary survey of normal human and rabbit blood (28), in both young and adult individuals, strongly suggested three tentative deductions: (1) That the lymphocyte is entirely comparable to all other blood-cells in that it arises under physiological conditions as a primitive undifferentiated cell, undergoes maturative changes, performs certain functions, undergoes senile degeneration, and has its viable life-span terminated by death and disintegration either in the blood or tissues; (2) that adequate maturative criteria (basophilia and mitochondria of the cytoplasm, chromatin density and distribution in the nonsegmented nucleus) sufficient for a determination of the approximate or relative age of any given blood lymphocyte within the span of its own life-cycle are available; and (3) that in health there is a relatively constant haemogram or proportionate representation of young (*Y*), mature (*M*), and old (*O*) types in the circulating blood, quite irrespective of a rather wide variation in total lymphocyte count. If the above interpretations from a study of the lymphocyte under normal conditions are correct, then an entirely new approach to a study of the diseases in which the lymphatic tissues are involved is opened up.

Prior to the present communication no survey has been accomplished in which an assay of both the qualitative and quantitative characteristics of the lymphocytes in tuberculosis has been attempted. Such a study has now for the first time become possible. It will be the purpose in this paper, therefore, to record our findings in a series of experimental and clinical studies and from their analysis to offer an explanation not only of certain of the past failures and discrepancies in the interpretation of the lymphatic reaction in this disease, but also to elucidate the apparent mechanism of the response as revealed by studies of the changes observed from time to time in the quality and number of the lymphocytes in the peripheral blood.

THE LYMPHOCYTE BALANCE IN HEALTH

Recent studies have conditioned the interpretation of adult haemograms in at least two respects. Careful, frequently repeated determinations upon the same individual (29) (30) have established the readily anticipated physiological fact that there is a constant independent ebb and flow from moment to moment of each type of blood-cell within certain "zonal limits" (31) characteristic of the individual (32) and his physiological status at the time of the observation. These published studies, abundantly confirmed in our subsequent observations, show the relatively greater instability of the lymphocytic when contrasted with the myeloid elements. Values ranging from 750 to 3,000 lymphocytes per cu. mm. have been found in health in entirely normal individuals, the proportion of *Y:M:O* forms in each instance being within the established limits for normal. These observations make simple quantitative determinations of lymphocytes of less significance than corresponding numerical estimates for the other cellular elements of the blood.

Although quantitative values fluctuate widely in health, equally marked variations in the qualitative characteristics of the cells do not seem to occur, unless disease is present to influence lymphopoiesis. That this same observation is true with respect to the granulocytes is now accepted, ample confirmation having followed the work of Arneth and Shilling. Our recent studies indicate that this essential and highly important principle applies with equal force to the blood lymphocyte. Thus, in the previously mentioned extremes of 750 and 3,000 total lymphocytes in two normal healthy adults, the qualitative haemograms (the proportion of *Y:M:O* forms) were each within the established range of normal for qualitative variations. It, therefore, seems highly

probable that, in the same sense that Arneth, and later Shilling, showed that a fixed formula of maturation stages exists for the neutrophile in health irrespective of the total cells, we may now present a similar qualitative formula or haemogram for the lymphocyte. While the estimated differences in the stage of cellular maturity of the lymphocyte are based on factors less readily and less sharply differentiated than those upon which the age of any given neutrophile is judged, there nevertheless may be recognized and segregated five distinct phases in the life cycle of the lymphocyte (28). For practical blood-counting, however, the information obtained by reducing the classification to three groups consisting of young (*Y*), mature (*M*), and old (*O*) cells is entirely adequate. It has been found (28) that in the average healthy adult the proportionate distribution of lymphocytes is *Y*:*M*:*O*::4:48:48. It is apparent that any accurate recognition of the lymphocytic balance in disease states must be conditioned by these observations which relate to both the quality and quantity of the lymphocyte characteristic in health.

GENERAL CONSIDERATIONS

Before any interpretation may be attempted, based upon variations in the circulating lymphocytes, certain other characteristics fundamental to this cell and to the tissue from which it takes origin must be recognized. The lymphatic tissue, unlike the bone-marrow, has a local nodal function to perform, as well as the more remote one of supplying cells to the circulation for wide functional distribution. Thus, we may conceive of local lymph-node reactions separate and distinct from the more generalized disturbances involving lymphocytic equilibria. The importance of this differentiation lies in the fact that studies of the blood frequently may not reveal the character of the tissue reaction, when it is sharply localized to one lymph node or one region. When, however, the motivating agent is of a nature so that a general lymphatic reaction is invoked, such for example as occurs in tuberculosis, the whole lymphatic tissue functions as an organic unit, as judged both from the peripheral blood and from direct examination of the various deposits of lymphatic tissue throughout the body. There thus exists a necessary dissociation of lymphatic responses: the one, focal in nature, often without accompanying blood changes; and the other, more or less generalized, in which the tissue changes within the lymph nodes are reflected in the peripheral blood by the lymphatic elements.

The generalized lymphatic reactions may be classified under three main headings: (1) Those associated with and secondary to generalized infectious processes; (2) those in which the basic pathological process is represented by a malignant hyperplasia of the lymphatic elements; and (3) those in which there is an apparent functional hypertrophy of nodal tissue unassociated with either demonstrable infection or neoplastic changes. Our present study has to do with the first of the above subdivisions, the infectious agent being the tubercle bacillus. In speaking of a more or less general involvement of the lymph nodes and lymphoid tissue in tuberculosis, we do not mean the actual formation of tubercles in every node, but rather the effect upon a variably allergized tissue of tuberculoprotein and other sensitizing fractions deriving from the metabolic processes involving the Mycobacterium in the body. In this sense the lymphatic tissues are among the most sensitive of the body, as they have been proved to be in the presence of many other insults, as for example, irradiation (33) (34) (35) (36), the pathogenic viruses (37) (38) (39), etc. It is thus a combination of two circumstances: the one, the demonstrated sensitiveness to tuberculotoxins (40) of the lymphatic tissues as reflected in the lymphocytes of the blood; the other, the known importance of lymphocytic round-cell infiltration in the circumscribing and delimiting of the tubercle in the tissues, which has made us feel that this first of the blood-elements to be linked with prognostic interpretations in tuberculosis, but the last to be fully evaluated in terms of modern haematological conceptions, is after all perhaps one of the most important single criteria upon which to base a judgment of the disease. We have arrived at this conclusion only after the accumulation and study of much experimental and clinical data, the analysis of many curves, and after a direct comparative study of all other data, obtained at the same time upon the same patients, which in the past have been thought to be of significance in the study of tuberculosis.

In order better to follow and understand the interpretation of the curves as they are presented, a brief discussion of certain of the theoretical considerations which have been derived directly from these studies must precede the actual data. Of the various factors that control or govern the number and character of the lymphocytes in the peripheral blood there would appear to be only four that are of major importance: (1) The speed and efficiency of differentiation and maturation of lymphocytes within the lymph nodes; (2) the rate of delivery of cells to the circulation; (3) the rapidity of their withdrawal or the degree of periph-

eral demand and destruction; and (4) the extent of the tissue storage of lymphocytes. It is a fair assumption from the evidence now available that the number of lymphocytic cells in the peripheral blood at any one time is a resultant of the balance of these forces.

There may be, however, a change in the proportional relationship of these several factors without any significant alteration in the total lymphocyte level. There are many total lymphocyte counts, in diseased states in which lymphatic involvement is known to exist, which are neither absolutely low nor abnormally high, and it is in this middle range, where at any given time an estimation of the total cells may not fully reveal the demands that are being made upon the lymphocytogenic tissues nor the adequacy of their response, that it is most important to determine the supply and demand from an analysis of the qualitative "shift" beyond the physiological limits of normal. Where the consumption or destruction of lymphocytes is rapid, there will be less time and opportunity for the full expression of the life-cycle of this cell and fewer of them will survive into the older (*O*) stage. The "O" type then serves as an "index of peripheral loss," in that when the percentage is seriously depressed below the lower limits for normal of these cells (30 per cent), the demand may be definitely recognized as abnormally great. If able to respond, the lymphopoietic centres promptly deliver increasing numbers of cells to the circulation, which is the avenue of distribution for peripheral consumption, and a younger type (*Y*) gradually becomes dominant, frequently assuming considerably higher relative percentages than the normal maximum limit of 15 per cent. This may be interpreted as a "reaction of regeneration." It must be obvious that the point at which a balance is struck between the two processes just mentioned will determine the level of total lymphocytes maintained in the blood-stream. When utilization or destruction exceeds replacements and is accompanied by a toxic depression of the regeneration centres for lymphoid elements, an absolute decrease in the circulating lymphocytes, particularly of Y and O types, results in a "reaction of degeneration." It has been the derivation and application of these interpretations to tuberculous disease which forms the basis of the present study.

THE LYMPHATIC REACTION IN EXPERIMENTAL TUBERCULOSIS

It is possible to compare and contrast every stage in the development and progress of tuberculosis, after having determined the normal equilibria of health during a suitable preinoculation control period in the experi-

mental animal. Our first detailed studies of the lymphocytic reaction in tuberculosis were, therefore, made on a series of 10 rabbits, each inoculated intravenously with 16,000,000 counted avian "S" acid-fast organisms (41) (42) (43) (44) (45) following control observations covering a period of from one to two months. Serial blood-studies were continued at weekly intervals until the fatal termination of the disease. Both

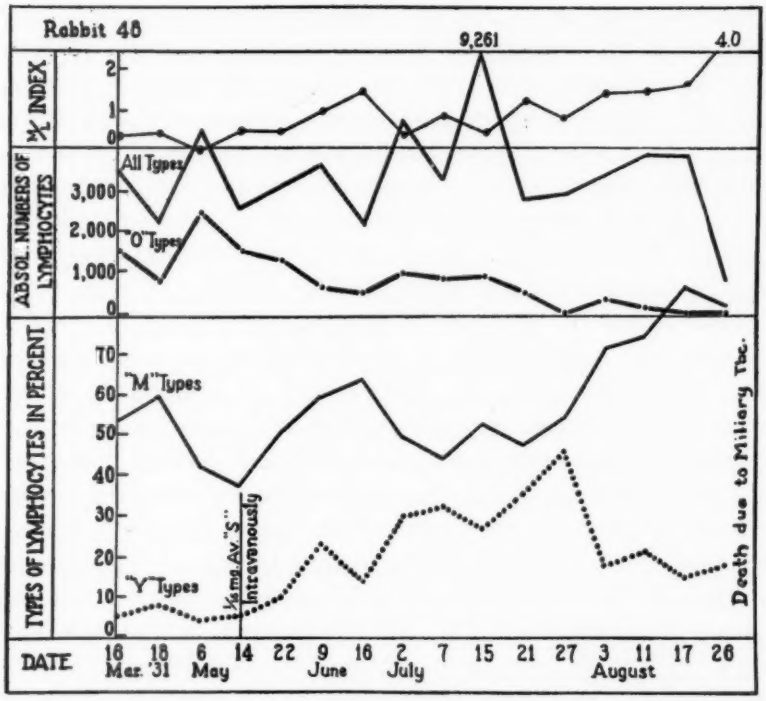

CHART 1. Progressive qualitative and quantitative changes in the lymphocytes of rabbit 48. This animal received 16,000,000 counted avian "S" organisms (1/16 mgm.) by intravenous injection on May 14. The top curve showing the M/L index is to be compared with the fluctuating values in the lymphocytes.

supravitally stained (neutral-red and Janus-green) films and cover-slip preparations stained by the Wright's-Giemsa technique were used for the differential count of the white blood cells, the total counts being determined by the usual techniques with Bureau of Standards glassware. The lymphocytes in this study have been classified on the basis of the differential criteria previously described (28), more especially the basophilia of the cytoplasm as revealed in carefully stained fixed films.

Equal numbers of cells from each of the two cover-slips were counted and averaged in determining the status of the reaction at any given time.

Charts 1 and 2 are representative of the course of events which occurred in this more or less fulminating disease produced by the virulent "S" type of organism. During the control period of one month for rabbit 48, chart 1, March 16 to May 14, the lymphocytes were present in normal total and qualitative proportions, that is, the distribution of lymphocytes between *Y*-, *M*-, and *O*-age types produced what we have designated as the composite "curve of normal reaction." However, almost immediately after infection, the percentage of young (*Y*) lymphocytes began to increase, reaching a maximum of 46 per cent on July 27. Such a progressive rise in the proportion of younger cells may be called the "curve of regeneration," and is significant of the response of the lymphatic tissues to an increased demand for lymphocytes. From July 27 to the time of the death of this animal one month later, a failing functional adequacy is reflected in a "curve of degeneration," with both young (*Y*) and old (*O*) lymphocytes rapidly diminishing in the circulation, together with a marked fall in the total lymphocyte count. This resulted in the development of a terminal monocyte-lymphocyte ratio of four to one, instead of the normal one to three.

A more detailed examination of the various related phases of the several curves in chart 1 suggests further interpretations of the mechanism of cellular reaction involved in the tuberculous process. During the period from the date of inoculation to June 16, though a definite rise in the young (*Y*) lymphocyte type was occurring, there is also to be noted a reciprocal fall in the number of old (*O*) forms per cu. mm. of blood, the moderate percentile increase in mature (*M*) cells being insufficient to overbalance the total lymphocyte count, which during this first period of the disease departed in no essential respect from the control period of the previous month. Thus, the increasing *M*/*L* index in this initial stage must have been, and was, due to an increase in the absolute number of monocytes in the circulation, which in turn was a reflection of the rapid proliferative response of monocyte-epithelioid cells with new tubercle-formation in the tissues. One of the essential pathological findings in a localized tubercle and one measure of body resistance is the characteristic "cuff" of lymphocytes which surrounds and effectively circumscribes the epithelioid-cell centre. To accomplish this limitation of an initial tuberculous "spread" of epithelioid cells effectively, the demand for lymphocytes, among other things, is immediate and urgent,

and during the first month of the disease in rabbit 48 the increased supply just equalled the increased demand so far as total turnover of cells was concerned, the only index of increased activity being the qualitative "shift" in these elements.

It would appear that during the second month, June 16 to July 15, one of the critical periods in experimental tuberculous infection in rabbits (46), the cellular defense elements gained a decided advantage. The decline in number of old (*O*) forms stopped, with a slight upward recovery and the subsequent establishment of a temporary plateau, indicating some decrease in the urgency of the demand from the tissues. A continuance, however, of the acquired accentuated momentum of replacement delivery of new cells from the lymphopoietic centres was evidenced by a steadily increasing percentage of young (*Y*) types. A rapid increase in total circulating lymphocytes from 3,000 to 9,200 per cu. mm. resulted during the month. That the lymphocytes exceeded the monocytes in proliferative activity during this period is further revealed in the lowered M/L index.

However, during the third month of the disease, despite a continued rise in the proportion of young (*Y*) lymphocytes to the highest peak yet attained (46 per cent), an increased peripheral consumption was heralded by the practically complete disappearance of all old (*O*) types from the blood, by a sharp decrease in the total lymphocyte count, and again by a rise in the M/L index.

With the beginning of the fourth month of the disease a new mechanism apparently entered the picture. Despite a high peripheral consumption of lymphocytes, suggested by the absence of old (*O*) cells in the blood and a relatively lower proportion of young (*Y*) regenerative types, the total lymphocyte count nevertheless showed a definite increase, the majority of the cells being mature forms. During the period represented by the counts on August 11 and 17, though the rate of regeneration (*Y*) was relatively lower, and the peripheral destruction (*O*) relatively higher than during the immediately preceding weeks, the total circulating lymphocytes were maintained at approximately 3,500 cells. However, it will be noted that just nine days later there was a precipitous fall in the total lymphocytes to less than one-third (884) of their former number with relatively no change in their qualitative relationships. A similar sequence of events has been noted in other of our cases of this disease, clinical as well as experimental, and the phenomenon described is believed to represent a final "agonal" effort to maintain the supply of

lymphocytes by the mobilization of mature (*M*) cell reserves from "storage" depots in organs and tissues such as the spleen and intestinal tract. The lymphocyte formula on August 26 may be considered then as representing the final failure of these cells and the lymphopoietic centres to adequately respond to the needs of the body, and this cellular collapse coincides with the failure of the animal to survive the disease.

The factor of mobilization and redistribution of mature lymphocytes from the many potential depots of the body, from time to time, is one that is difficult and at times impossible of evaluation separately from the other influences already mentioned as interacting to affect the peripheral count. It is undoubtedly true that a single isolated determination may be subject to misinterpretation through the transitory domination of redistribution and mobilization influences, as for example Barcroft's (47) demonstration of the influence of erythrocyte reservoirs in the spleen on the peripheral erythrocyte concentration. It is apparent, however, both from the factual evidence we have obtained as well as from the common knowledge of the mechanism involved in such vasomotor phenomena, that sustained trends, as revealed in repeated determinations over a definite period of observation in the same individual, are little if at all affected in their interpretation by the operation of this factor. The curve of *M* types, when taken over a given period of time, in conjunction with total lymphocyte count, and *Y* and *O* forms, is probably the best measure of this reserve factor for the lymphocyte. Again is demonstrated and emphasized the importance, to the adequate interpretation of all blood data, of more than one determination and of a more than casual cellular differentiation: the more observations available and the more completely differentiated the cells, the better the knowledge of the state of health of the individual.

As might be expected, the more acute the tuberculous process the less marked and the less significant are the cellular changes just described. Toxic and allergic phenomena assume a major and predominant rôle both in the clinical picture and as the immediate cause of death. Chart 2 outlines the blood changes pertinent to this study in such an acute miliary process of seven weeks' duration induced in rabbit 49 by the same dose of the same culture and suspension of "S" avian tubercle bacilli used in the previously cited animal. A definite change in the trend of the *Y*, *M*, and *O* curves is readily noted, dating from the day of inoculation. During the first 19 days of the disease some increase in the delivery of new cells (*Y*), perhaps some increased mobilization of

stored lymphocytes, *M*, with no apparent diminution of the older elements in their absolute representation, resulted in an elevation of the total circulating lymphocytes to a value approximately double the pre-inoculation level. However, coincident with a sharp increase in the peripheral consumption of lymphocytes, as reflected in a precipitous fall in the older (*O*) types, there occurred a fall in the total lymphocyte

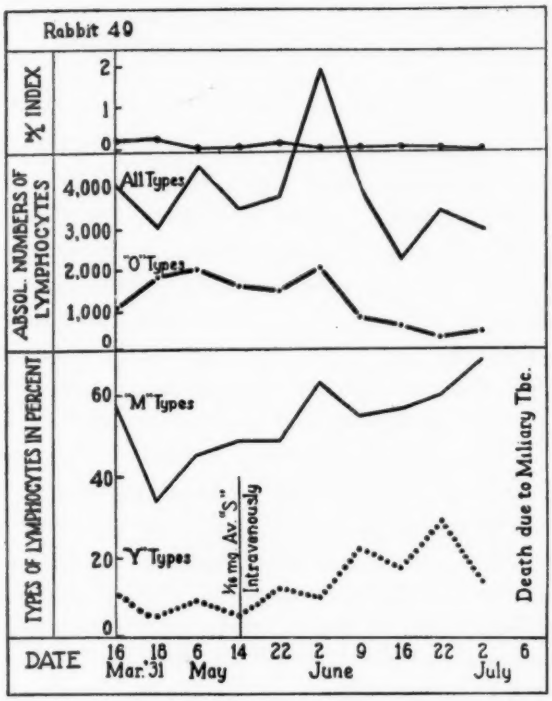

CHART 2. Progressive qualitative and quantitative changes in the lymphocytes of rabbit 49. This animal received 16,000,000 counted avian "S" organisms (1/16 mgm.) by intravenous injection on May 14. The top curve showing the *M/L* index is to be compared with the fluctuating values in the lymphocytes.

level from 7,500 to 2,500 in the succeeding two weeks. Though the lymphopoietic centres indicate a moderate effort at regeneration (*Y* curve), the mobilization of mature lymphocytes (*M*) seems to have been the more important source of supply of cells for maintaining the peripheral count at the various levels noted in the graph. The maintained low monocyte-lymphocyte ratio is further evidence of the predominance of the toxic elements (tuberculoprotein and polysaccharide as contrasted

with tuberculophosphatide products (2) (40) (48)), in this instance, the qualitative "shift" in the lymphocytes being the only significant cellular reflection of the reaction. It is possible that constitutional defects or subclinical disease other than the tuberculosis *per se* may have contributed to the rapid course of events leading to death in this animal, but the finding of widespread miliary lesions postmortem, and a knowledge of the acute toxaemia, or haemorrhage, which may suddenly terminate the tuberculous process, make it equally plausible to explain the outcome as directly the result of the uncomplicated disease.

THE LYMPHATIC REACTION IN HUMAN PULMONARY TUBERCULOSIS

A group of hospitalized patients in the Franklin County Tuberculosis Sanatorium, Columbus, Ohio, was carefully selected, in coöperation with the medical personnel of the institution,[3] for this special clinical study. In addition to the cytological studies already outlined, it was desired to apply as many as possible of the various criteria, which have been reported as of value in the study of clinical tuberculosis, to the same patients at the same time, and thus perhaps reëvaluate them in relative terms. For this purpose patients were chosen representing at the time of initial selection each of three arbitrarily classified stages in the disease: (1) early minimal lesions, (2) moderately advanced disease, and (3) far-advanced tuberculosis. The classification was that generally accepted at the present time and based largely upon X-ray evidence, supplemented by clinical and laboratory data as outlined in the accompanying charts. All patients were under routine sanatorium care but were subjected to no special therapeutic procedures during the period of this study.

Repeated examinations were made at regular intervals covering the following points: (1) complete blood-studies, utilizing both supravital and fixed techniques, were made personally by the authors at weekly intervals during the six months' period of the study; (2) serial X-ray plates were taken at two- to four-week intervals; (3) careful nursing and bedside clinical notes were made daily by the attending staff and checked weekly by the authors, the sum-total of these data being used as the basis for the generalizations made on "Physical" status of the patient in the charts; (4) the patients were weighed twice weekly; (5) the eryth-

[3] Grateful acknowledgment is made to the late Doctor C. O. Probst and to Doctor M. D. Miller of the Sanatorium staff for their valuable coöperation and assistance, generously offered throughout this study.

rocyte stability was measured as the sedimentation velocity in Wintrobe tubes twice monthly; (6) the haemoglobin estimations (Newcomer) were made weekly and, as has been pointed out elsewhere (49), are of much greater significance than the total red cell count in assaying tuberculous activity; (7) numerical Gaffky and morphological studies of the acid-fast bacilli in the sputum-positive cases, and single colony petri

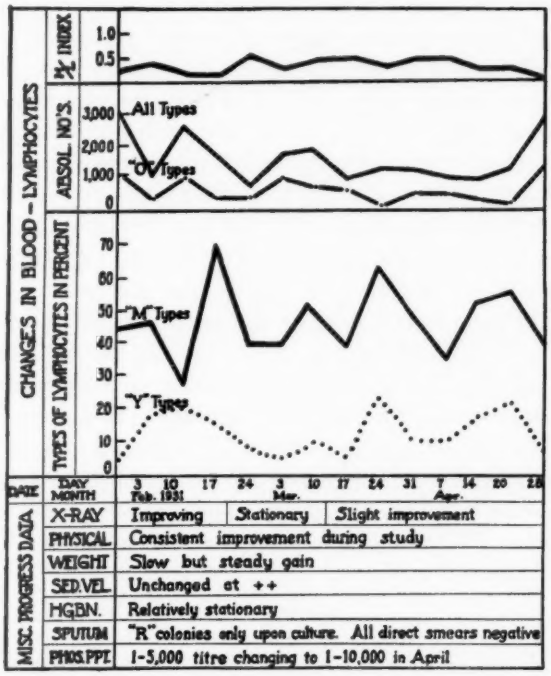

CHART 3. Progressive qualitative and quantitative changes in the lymphocytes of patient R. N. A summarization of data showing the progress of the case, together with related changes in laboratory tests, is shown directly below and chronologically with the fluctuations in the lymphocytes. The M/L index is given for comparison of the monocytes with the lymphocytes.

dish cultures (Petroff), were made every two weeks on Petroff's gentian-violet-egg medium; (8) on alternate weeks with the sputum examinations phosphatide precipitin tests according to the technique devised by one of us (C. A. D.) (50) (51) were run on the blood-serum from each patient.

For the sake of conciseness and clarity of presentation we have attempted to reduce this mass of data in each case to one chart, chronologically and directly comparable. We have likewise chosen to present

and discuss from the three clinical categories studied only a few selected cases which are typical of the different types of reactions we have encountered and which include the evidence upon which our conclusions are based.

R. N., a young married woman, aged 26, was known to have had a tuberculous infection for six years and had been in the sanatorium seven months prior to this study. The X-ray lesion was classified as moderately advanced, but the clinical and laboratory evidence suggested minimal activity in February, 1931, and during the following six months the clinical course was consistently that of progressive improvement (chart 3). All sputum examinations were negative for acid-fast organisms, and on only one of the many petri-dish cultures planted during this six-month study were three "R" colonies of typical tubercle bacilli grown. During this period the ability of this patient's blood-serum to flocculate tuberculophosphatide increased from an original titre of 1–5000 to 1–10,000. An analysis of the lymphocyte findings, as recorded in chart 3, reveals a balance not unlike that observed in the normal nontuberculous individual. The total lymphocyte count during the greater part of the period remained under 2,000 cells per cu. mm., which is the minimal critical level for normal arbitrarily set by Medlar (8), and to that extent might be interpreted as of unfavorable prognostic significance. However, the qualitative differential shows a composite curve of lymphocyte response sufficiently similar to the "curve of normal reaction" to be quite reassuring. On three occasions, February 10, March 24 and April 20, an increased turnover of lymphocytes was apparent through a lowering of the old (*O*) cells, and a prompt regenerative response of moderate degree and brief duration of the young (*Y*) types.

We interpret these phenomena as evidence of an effective cellular resistance to subclinical exacerbations of the disease. The M/L index remained under 0.5 during this period, which is in accordance with the high phosphatide precipitin titre already mentioned, and which usually guarantees no new tubercle-formation and no progressive epithelioid differentiation. A critical analysis of the lymphocytes in this case, then, confirms the relative resistance of this patient to her disease, at the same time furnishing presumably a more delicate index of small potential relapses than any of the other observations. That this prognosis was justified is borne out by the subsequent history of the case. Shortly following this study the patient successfully survived a pregnancy, and at the time of this writing, two and a half years later, although living at home under anything but ideal conditions, she does not show any appreciable extension of her pulmonary lesions.

A somewhat less effective resistance to her tuberculous disease than that just observed is evident in the case of

V. S., a young white woman, aged 18, was classified at the beginning of this study, on X-ray evidence, as FA-A, the duration of the disease being four years. The struggle for supremacy between the defense forces of the body

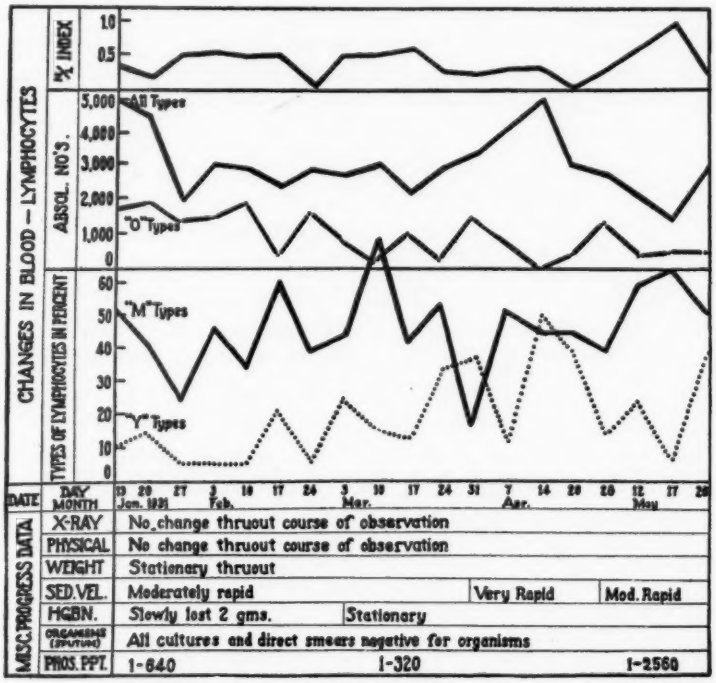

CHART 4. Progressive qualitative and quantitative changes in the lymphocytes of patient V. S. A summarization of data showing the progress of the case, together with related changes in laboratory tests, is shown directly below and chronologically with the fluctuations in the lymphocytes. The M/L index is given for comparison of the monocytes with the lymphocytes.

and the invading microörganisms is quite apparent from an analysis of the data on chart 4. During the first month of the study the lymphocytic equilibrium was approximately normal, the decrease in total lymphocyte count during this time being a reflection of the mature (M) types and a mobilization phenomenon probably. However, between the 10th and 17th of February a marked change occurred in this qualitative balance of the lymphocytes with no reflection in the total lymphocyte count. The peripheral consumption was

apparently sharply increased (drop in old (*O*) types) with an attempt both at regenerative (*Y*) and mobilization (*M*) compensation. The sensitiveness of the redistribution response and the adequacy of the reserves of mature lymphocytes in the organs and tissues in this patient is indicated, first, by the high level of total lymphocytes without a high proportion of young (*Y*) cells, found on first examination in January; and, second, by the rising percentage of mature (*M*) cells noted between January 27 and March 10 against a falling number of old (*O*) forms, which was adequate to maintain the level of lymphocytes in the peripheral distributing pathways at approximately 3,000 cells per cu. mm. A gradual regenerative "shift" further reflected the exacerbation in the disease, reaching its climax on April 14, when fully 50 per cent of the 5,000 lymphocytes then found in the blood-stream were young (*Y*) cells, with a complete absence of the older (*O*) stages. At this time the only other evidences of an increased activity of the disease process were to be found in an increase in the erythrocyte-sedimentation rate, and a decrease in the phosphatide precipitin titre. The *M/L* index gradually fell from March 17 to April 20, indicating the effective domination of the lymphocyte response over the stimulus to monocyte proliferation. However, with the subsidence of the lymphatic-tissue response, the total lymphocytes fell, and the monocyte-lymphocyte ratio promptly rose to 1.0. This segment, then, out of the midst of the long struggle for health in this patient, indicates the insecurity of the equilibrium which was being maintained by an as yet unusually responsive lymphatic tissue, but such reaction should greatly encourage the institution of fresh measures of assistance to the defense forces of the body with real promise of ultimately limiting the malignancy of this tuberculous process. This patient, intractable to management, died two years after the conclusion of this study from a pulmonary haemorrhage, sustained during an automobile trip to a sanatorium in the West.

One of the most interesting and instructive cases in the entire series, from the standpoint of the sensitivity of the lymphocytic index of tuberculous activity and body resistance, was that of

W. I., a young white male, aged 22, with known tuberculosis of three years' standing, and a sanatorium history of eleven months. The X-ray films in January, 1931, showed a far-advanced tuberculosis with cavities, and evidence of marked activity of the disease; the clinical findings were in accord with the laboratory data (chart 5).

The *Y:M:O* relationships of the lymphocytes in the peripheral circulation during the first five weeks of observation showed a sustained composite "curve of regeneration," the young (*Y*) cells (40–50 per cent) showing a sufficient response of the lymphatic tissues to maintain the total count at 2,000 cells per

cu. mm. with the representation of old (*O*) types indicating only a moderately increased rate of peripheral consumption. The *M/L* index at approximately 0.33 also affirmed the equilibrium of the cellular balance during this period. However, starting about February 10, something occurred to markedly upset this cellular equilibrium, the young (*Y*) cells rising sharply from 30 to 50 per cent, with a reciprocal reduction in older (*O*) types, followed immediately

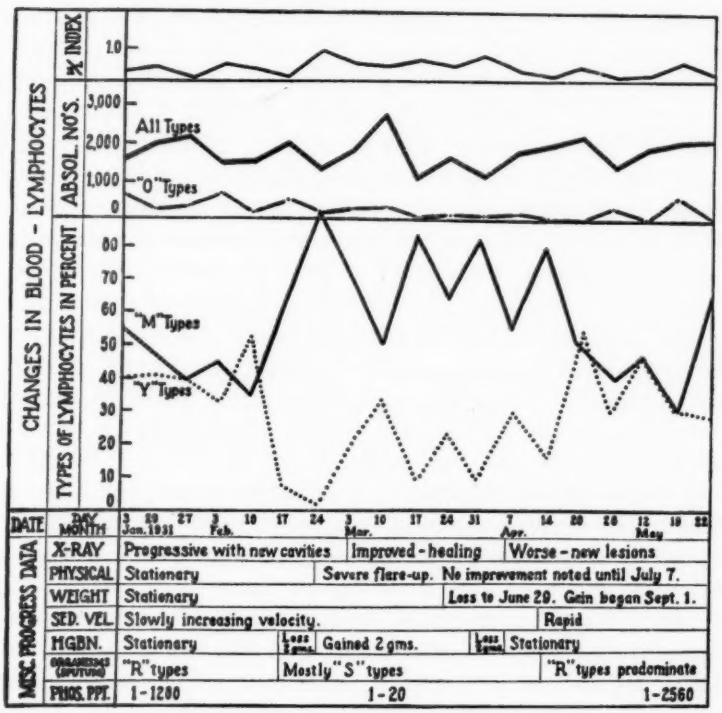

CHART 5. Progressive qualitative and quantitative changes in the lymphocytes of patient W. I. A summarization of data showing the progress of the case, together with related changes in laboratory tests, is shown directly below and chronologically with the fluctuations in the lymphocytes. The *M/L* index is given for comparison of the monocytes with the lymphocytes.

during the next two weeks by an almost complete paralysis of the lympho-poietic-delivery mechanism for new cells, which up to this time had been functioning most efficiently. Though the total lymphocytes showed little if any change from the zonal level previously maintained, due to the response of mature (*M*) cells in the emergency, the *M/L* index rose sharply to 1.0, indicating an increased proliferation of epithelioid cells in the tissues, with an absolute increase of monocytes in the peripheral circulation. No clinical evidence

of the changed status in the disease was apparent until February 24, when the patient became definitely sicker subjectively, with fever and pulse changes, a loss of 2 gm. in haemoglobin, increased numbers of acid-fast organisms in the sputum with the appearance of "S" type colonies on direct culture, and the loss of the power of his blood-serum to flocculate tuberculophosphatide. All of these changes could mean just one thing in the light of our present knowledge: that is, a sudden release from a focus in the lung to the general circulation of the products of interaction between Mycobacterium and tissues, the toxic tuberculoprotein and polysaccharide (40) (48) substances producing the lymphopoietic paralysis, fever, tachycardia, and subjective symptoms and objective signs of collapse; and the tuberculo-lipoids (2) stimulating new epithelioid-cell differentiation. Such an accident frequently ends fatally for the patient and such an outcome was anticipated in this instance by all who saw the severity of the clinical reaction. However, the regenerative resiliency of the lymphatic tissues in this patient became apparent just one month after the first cytological evidence of the onset of the crisis just described, and within two weeks after its greatest cellular reflection and the appearance of clinical symptoms. On March 10 the proportion of young (*Y*) cells in the circulation had rebounded to 30 per cent, carrying the total lymphocytes to 3,000, their peak point during the six months period of this study, the old (*O*) cells remaining present in sufficient numbers to indicate the central toxic nature of the disturbance in lymphocytic equilibrium up to this point. The gradual recovery of lymphopoietic efficiency and the increased peripheral consumption of the returning lymphocytes with evidence of their effectiveness in again limiting monocyte-epithelioid proliferation is shown in an analysis of the curves from March 17 to April 20, in which a falling *M/L* index and a return of the young (*Y*) types to around 40 per cent heralded the reëstablishment of a cellular equilibrium similar to that observed in January. Though this cytological balance of favorable prognostic significance was reattained by April 20, no clear-cut evidence of clinical improvement was noted until July 7, and there was no gain in weight until September. However, during May the "S" type colonies of acid-fast organisms disappeared from the sputum cultures, and the phosphatide precipitin titre of the blood serum returned to 1–2,560, further substantiating the improving immunological basis for subsequent clinical and symptomatic improvement. This patient continued to remain in precarious though definite equilibrium with his disease until November 30, 1932, when a sudden pulmonary haemorrhage proved fatal.

Such a study as this suggests several points worthy of note. First, it confirms the importance which has come to be attached to the *M/L* index as reflecting, and not infrequently prognosticating, tuberculous activity; second, the total lymphocyte curve varying between 1,500 and

3,000 cells per cu. mm. adds nothing of itself to our information; third, an analysis of the proportional qualitative variations within the lymphocyte group, if interpreted upon the basis of lymphopoietic activity as understood by us, does provide a far more sensitive indication of events to come, both in relapse and in recovery, than any yet described; fourth, it permits differentiation between a central toxic effect (February 10 to March 10) and a peripheral cellular struggle in the tissues with minimal general toxic manifestations (March 17 to May 19); fifth, such interpretations of the lymphocytic changes may be permitted and are justified not alone upon the theoretical basis of what is now known of the similarity which exists between myelopoietic and lymphopoietic reactions, but from the numerous evidences accumulated by a variety of techniques of the actual sequence of events in this patient which such interpretations predicted and substantiated; sixth, in a patient with this demonstrated inherent resiliency of cellular and humoral defense mechanisms, the success of measures directed toward a limiting of the opportunity for sudden dissemination of toxic products, or fatal haemorrhage; that is, the surgical elimination of cavities, is strongly indicated. Such studies with such measures are at present under way in this department.

Chart 6 illustrates the data in the case of

a young woman, J. T., aged 20, with a progressive downhill course, and finally death, during the months of observation. This patient showed evidence of marked clinical activity, with roentgenological findings of far advanced (FA-C) tuberculosis. The trend of the composite lymphocyte curves was that of a progressive degenerative "shift," from the time the observations were begun until the termination of the disease. During January the temporary reappearance of the old (*O*) cells coincident with a falling percentage of young (*Y*) types in the blood might have suggested the subsidence of an active phase, but the M/L index continued around 1.0 and both *Y* and *O* cells progressively decreased during the last two months. The total lymphocytes fell to well under 1,000 per cu. mm. during the last two weeks of life, the M/L ratio rising to 2.0. All of the correlated studies (chart 6) reflected the progressive nature of the tuberculous process, with practically no evidence of either humoral or cellular defense. Many "S" type acid fast colonies were present on every sputum culture.

Lymphocytic changes, almost identical with those just described, were seen to develop and progress in another patient,

R. A., aged 19, during the last five months of his tuberculous disease. The X-ray diagnosis was FA-C. Rather wide variations in the proportion of young

(*Y*) cells found during January suggests the attempt on the part of the lymphopoietic centres to overcome the toxic depressant element. However, from February on there was a gradual but constantly diminishing level of *Y*- and *O*-type lymphocytes in the blood-stream, the "curve of degeneration," the

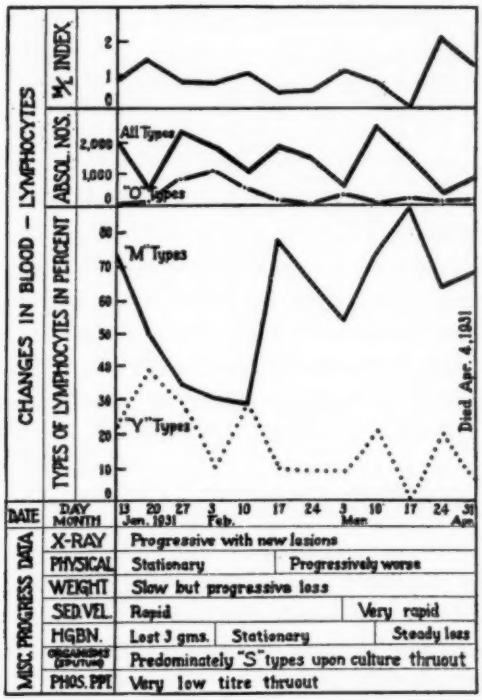

CHART 6. Progressive qualitative and quantitative changes in the lymphocytes of patient J. T. A summarization of data showing the progress of the case, together with related changes in laboratory tests, is shown directly below and chronologically with the fluctuations in the lymphocytes. The *M/L* index is given for comparison of the monocytes with the lymphocytes.

M/L index being as a rule very high (6.5 on March 17). The data are summarized on chart 7.

THE COMPARATIVE VALUE OF VARIOUS CLINICAL AND LABORATORY DETERMINATIONS IN THE STUDY OF CLINICAL TUBERCULOSIS

Only by a careful study of the same patients over a long time, utilizing well-established and generally accepted objective criteria as a basis for judgment of the progress of the disease, may any new method for the

interpretation and prognostication of events be measured. It was thus necessary to consider each case from every possible angle before attempting to analyze and interpret the cellular changes here presented. Many studies have been made to prove the value of a particular determination, such, for example, as the erythrocyte-sedimentation rate in an attempted

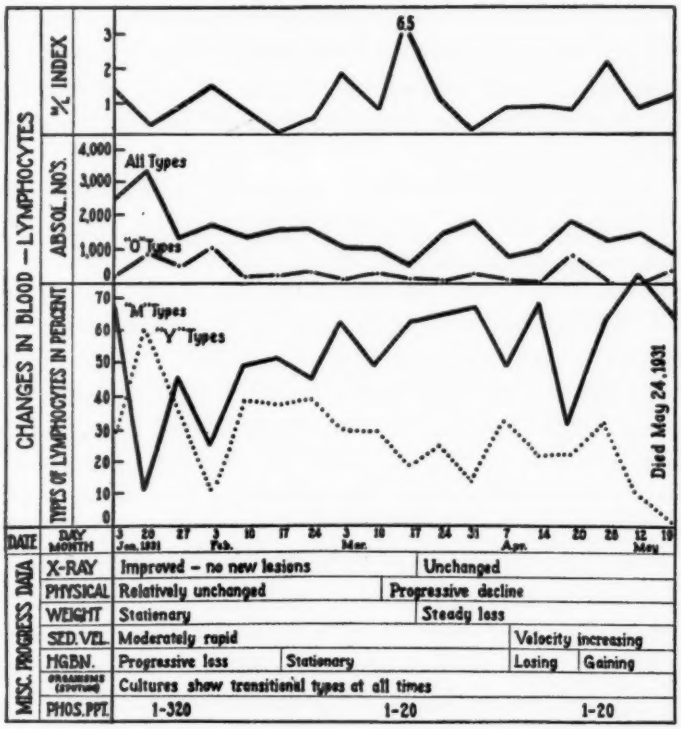

CHART 7. Progressive qualitative and quantitative changes in the lymphocytes of patient R. A. A summarization of data showing the progress of the case, together with related changes in laboratory tests, is shown directly below and chronologically with the fluctuations in the lymphocytes. The M/L index is given for comparison of the monocytes with the lymphocytes.

estimation of the amount and degree of activity in tuberculous disease. Our objective in this study was twofold: First, to study not one but many different procedures in the same individual at the same time over a sufficient period to determine their relative merits as reflectors or predictors of the disease-process; and, second, with these as controls to compare and contrast a new procedure, that of the application of the

qualitative analysis of the lymphocyte to tuberculous disease. The various determinations carried out in this study have been the most depended upon of the techniques now universally used in the study of tuberculosis. Our X-ray evidence in each case was adequate and unequivocal in so far as that technique may be applied to a study of the progress of the disease. Serial stereoscopic plates were made on all patients in this series. A confirmation of the usual information to be derived from repeated physical examination, weight-curves, quantitative blood studies and sedimentation velocity was obtained. Special comment may perhaps be limited, therefore, to the remaining three determinations.

We have found repeatedly that in progressive tuberculosis the haemoglobin level gradually falls, usually with the total red-cell count remaining at approximately 4,000,000. Frequently we have observed a steady decrease from 12 or 13 gm. per 100 cc. blood to 6 gm. in a period of from four to six months, the red-cell count remaining unchanged, and always associated with progressive disease. Unpublished studies from our laboratory by Dr. D. E. Yochem, based upon this observation, have indicated that in some cases iron, and in others iron in association with the secondary anaemia fraction of liver, may be able to correct this hypochromic microcytic anaemia secondary to the active tuberculous process.

The dissociation of the tubercle bacillus into rough "R" and smooth "S" colonies with varying degrees of pathogenicity may be said to have been amply confirmed since Petroff's original work. However, it is to be remembered that these terms are arbitrary and represent in the strictest sense the extremes of a whole succession of intermediate stages. We have classified the colony structures obtained in these sputum cultures under three headings: (1) "R," relatively less virulent, rough, dry, large chromogenic colonies; (2) "S," relatively more virulent, smooth, moist, small, nonchromogenic colonies; and (3) "T," transitional stages between these two; fairly virulent, flat, moist, irregular, nonchromogenic colonies. In no patient dying while under observation did we fail to find a predominance of either "S" or "T" type colonies on sputum culture. Characteristic of the more chronic stages were the "R" colonies. In certain cases experiencing exacerbations of the disease with recovery during the period of observation, as for example see chart 5, a change in the type of colony was conspicuous, the "S" type dominating during the exacerbation. That the type of organism rather than the number pres-

ent in the sputum determines the seriousness and severity of the disease at a given time seems a justified conclusion to us from both experimental (43) and clinical studies.

The phosphatide precipitin test is a measure of the flocculating capacity of the blood-serum of tuberculous patients for tuberculolipoids, specifically the phosphatide A-3 of Anderson (52). Since the fatty-acid active principle in tuberculophosphatide has been shown to carry the major stimulus to monocyte-epithelioid stimulation in the tissues (40), when its neutralization by the body-fluids is at a maximum the spread of tuberculous lesions should be at a minimum. The application of the test in these studies would seem to have further confirmed this interpretation of the reaction.

THE RELATION OF THE LYMPHOCYTE REACTION TO PROGNOSIS IN TUBERCULOSIS

Tuberculosis is a highly complex disease in which at all times there are innumerable factors entering into and having a direct bearing upon the outcome. Complications, either of tuberculous or of nontuberculous origin, may change the balance at a given moment, suddenly and unexpectedly, as for instance in the case of pulmonary haemorrhage. It is therefore to be emphasized that any attempt at prognosis, using what criterion one may as a basis, must be conditioned upon this uncertainty.

Properly evaluated, however, and taken together with other relevant data, we believe from our studies that the lymphocytic reaction is as true and sensitive a measure of the immunological reactions of the tuberculous individual as has been developed. This is particularly true if a goodly series of accurate, qualitative observations is available for interpretation. It is, of course, obvious from the clinical and other laboratory data in this series that the total lymphocyte count is no measure of the resistance of an individual to his disease. On the other hand, a recognition of the cytological criteria necessary to estimate the relative age of the individual lymphocyte in the peripheral circulation, and an understanding of the fundamental facts underlying lymphopoiesis, provide the basis for analyzing and interpreting the changes which occur from time to time in terms of the functioning of the mother tissues. Thus, with a cellular partition that is maintained with *Y*-, *M*- and *O*-type percentages approximately normal the prognosis is good. If, under increased demand for lymphocytes, the percentage of young (*Y*) cells increases faster than the peripheral consumption, "curve of regenera-

tion," and the total count is sustained or elevated, a favorable equilibrium is indicated. A high peripheral consumption or destruction of lymphocytes, associated with a failing regenerative delivery of new cells to the circulation and tissues, "curve of degeneration," is significant of a failing cellular defense with consequent bad prognosis. These qualitative lymphocytic changes appear some time prior to any other indication of change in the status of the patient.

THE RÔLE OF THE LYMPHOCYTE IN TUBERCULOSIS

The belief that the lymphocyte is a specific resistance factor in tuberculosis has been inferentially based on two observations: (1) Upon the frequent association of regressing lesions and a high relative and absolute percentage of lymphocytes in the peripheral blood; and (2) on the histopathological picture of the tubercle with its outer encircling "cuff" of lymphocytes suggestive of a mechanical, and perhaps more subtle, limitation of spreads of the central epithelioid cells harboring the Mycobacterium.

While the majority of the investigators believe these associations to definitely place the lymphocyte in the category of an active defense agent against the disease, there has been no unanimity of opinion as to just how this cell performs its function. The early observations of Webb (11) (12) (16) and the later experimental studies of Murphy and coworkers (53) (54) (55) were interpreted as evidence of direct defense action. However, Smithburn (56) has recently shown that the longevity of rabbits inoculated with bovine tubercle bacilli following lymphocytic stimulation with foreign protein injections was less than the controls. Gardner (57) has called attention to the fact that the lymphocyte *per se* has never been proved definitely to protect against tuberculosis and suggests that the lymphocytic reaction when it occurs is a reflection of the allergic state. Cunningham and Tompkins (58) point out the possible influence of lymphotoxins on the lymphocyte level, and, while agreeing that this level in the blood seems to parallel resistance closely, suggest that the lymphocyte may have a passive rather than an active rôle in the struggle against the infection. Maximow (59) presents still another viewpoint in his interpretation of the lymphocyte as a stem-cell for the differentiation of monocytes and epithelioid cells in tuberculosis.

It is believed that the analysis of the lymphatic reaction in the experimental and clinical studies here reported tends to clarify some of the conflicting interpretations of previous investigators and lends additional

evidence in support of the hypothesis that the lymphocytes are in themselves actively resisting factors in tuberculosis. The demonstration that there may occur a high degree of regeneration of these cells, without concomitant high numerical levels and with the virtual disappearance of old types from the blood-stream, strongly suggests the utilization or consumption of these elements in the pathological process. Furthermore, regardless of the degree of regeneration, if the peripheral numerical level of lymphocytes is not maintained, the patient does badly, and invariably dies if rapid peripheral consumption coincides with a failure of regenerative activity. These observations all point to the importance of an adequate supply of these cells if the disease is to be held in check. While the toxic element enters into the picture, at times paralyzing the lymphopoietic centres usually temporarily (see chart 5), such an influence can hardly explain the association of active regeneration, a positive numerical cellular balance and favorable clinical progress. Just as the bone-marrow may be paralyzed by an overwhelming toxaemia, though its ordinary response to infection is one of increased delivery of cells with a "shift to the left" in its granulocytic product in the peripheral blood, so the lymph nodes would seem to respond in tuberculosis with a regenerative "shift," except rarely when overwhelmed by an unusual toxic flood or exhausted by the long-continued chronic drain of the disease.

SUMMARY AND CONCLUSIONS

1. In this study an analysis of the qualitative changes occurring in the lymphocyte, which we believe reflect directly the functional state of the lymphopoietic centres, has been applied to disease. For various reasons tuberculosis, in its experimental and clinical phases, furnished the best initial test of this hypothesis.

2. In the experimental studies it has been possible to follow in a single animal the entire natural history of the disease. A varying efficiency in the response of the lymphatic tissues from time to time was reflected by the changes in the circulating lymphocytes, which in turn seemed to represent a very fair measure of the adequacy of the general immunological reactions of the animal. A judicious interpretation of both quantitative and qualitative data is essential to the fullest understanding.

3. A careful selection of patients representative of the various stages of the disease has provided a basis for a similar analysis of the lymphatic reaction in clinical tuberculosis. In these studies the lymphatic response

has been far more sensitive, and has preceded other evidence of a changed status in the disease more consistently than any other criterion thus far used. It may thus be of distinct prognostic significance.

4. Additional evidence is furnished in these studies of the direct part played by the lymphocyte in the cellular defense of the body against tuberculosis.

5. It is desirable to have as many criteria as possible in the analysis of any given tuberculous case, and even so the frequency of unexpected complications always renders prognosis hazardous. In a comparative study of a number of different determinations upon which reliance has been placed in the past, something more of their relative merits has been ascertained. More specifically, the following of the haemoglobin level, a study of the quality, "R" versus "S" colonies, rather than the quantity of the acid-fast organisms present in the sputum from time to time, and the determination of the titre of the phosphatide-precipitating capacity of the patient's blood-serum, have yielded much valuable information in this study.

6. Emphasis, finally, is to be placed upon repeated examinations in the same patient, with exquisite technical precision rather than a single casual observation, if the full significance of any procedure is to be realized. Tuberculosis ordinarily runs a long chronic course with exacerbation and remission and with gradual trends rather than a stationary equilibrium. Therefore, a better understanding of the inherent resistance forces, and more particularly their full conservation by appropriate adjuvant measures, in the individual patient, is essential at the present time for the intelligent management of the disease.

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THE RÔLE OF ATELECTASIS IN PULMONARY TUBERCULOSIS[1,2]

BARNET P. STIVELMAN

The effect of atelectasis on tuberculous lung foci has only recently evoked clinical interest. This is due to the fact that the aetiology of atelectasis has been firmly established only within the past few years. It is now generally agreed that the essential cause of atelectasis in any lung area is the complete obstruction of its draining bronchus. Moreover, it has been shown that the contributory factors are of importance only in that they favor bronchial obstruction. Among these are:

(1) Inflammatory processes in the larger or smaller bronchi, causing accumulation of viscid secretion, which interferes with normal function of the ciliated epithelium.

(2) Pain in the chest or lower abdomen which causes shallow respiration.

(3) Administration of narcotics to ease pain which abolishes the cough-reflex, and so militates against adequate pulmonary ventilation and drainage.

(4) The prone position which interferes with the normal respiratory function.

A consideration of the factors just enumerated justifies the suspicion that atelectasis in tuberculosis is of much greater frequency than the literature on the subject would indicate. The growth of granulations in the smaller bronchioles, the ever-present viscid secretion emanating from the bronchi and caseous parenchymal processes, the frequent haemoptyses, the treatment of the disease with rest in bed and suppression of cough, and the induction of pneumothorax, all tend to interfere with normal bronchopulmonary ventilation and drainage and eventually lead to atelectasis in the tributary lung area. Indeed the opportunities for atelectasis are so constant and numerous that it may justly be doubted that a tuberculous lung is ever free from it.

With a view to determine the influence of atelectasis on the progress and involution of tuberculous lung foci and particularly its relation to fibrosis and healing in the course of collapse therapy, the films of more

[1] From the Medical Service of the Harlem Hospital, New York City.

[2] Read at a meeting of the Section of Medicine, New York Academy of Medicine, March 21, 1933.

than 5,000 patients treated under my supervision in the past eight years were carefully reviewed. This paper is based on the data thus obtained.

ACUTE MASSIVE ATELECTASIS

Acute massive atelectasis is relatively uncommon. It was observed but four times,—all in cases of severe haemoptysis. The surprising rarity of this complication in view of the frequency of haemoptysis in phthisis is undoubtedly due to the fact that patients who bleed are not often carefully examined physically or roentgenographically.

In most instances it is the bronchus draining the bleeding lung which is obstructed, and the process may be a salutary one, as it unquestionably helps the tamponage of the bleeding vessel. Occasionally it is the contralateral bronchus that is plugged, and then the dyspnoea may be marked and the patient's life endangered as in one of our cases reported elsewhere (1).

The posthaemoptoic tuberculous bronchopneumonias, about which we heard much in years gone by, are in reality atelectases of varying degrees due to the aspiration of the blood into the smaller bronchi of the neighboring lung area. As a matter of fact, lobular atelectasis is almost invariably observed in cases subjected to careful roentgenological examination within the first few days following haemoptysis. These shadows clear rapidly if cough is not unduly suppressed by the administration of narcotics and the patient is put in a semisitting position to encourage normal respiration.

CHRONIC MASSIVE ATELECTASIS

The chronic type of lobar and multilobar atelectasis in tuberculosis is of great clinical interest. I shall not consider the atelectasis due to pressure of tuberculous lymph nodes on the bronchi. This has been thoroughly discussed by Lerche (2), Simon and Redeker (3) and others.

Of greater importance is the form of chronic massive atelectasis associated with tuberculosis in young persons who pursue a chronic course uninterrupted by frequent periods of activity, who are usually above normal in weight, whose sputum shows few tubercle bacilli, and whose lesion remains preponderately unilateral. They rarely have tuberculous complications and would enjoy good health were it not for secondary bronchiectasis that develops as a result of cirrhosis of the lung.

There are no reliable data to show whether this apparently providential atelectasis and the subsequent cirrhosis are due to an old primary plug-

ging of the main bronchus or to multiple lobular atelectasis which has slowly progressed so as to involve ultimately the larger and main bronchi.

Chronic massive atelectasis of the lung in phthisis is most often confounded with extensive unilateral pleuropulmonary fibrosis. Mistakes can be avoided if it is remembered that extensive tuberculous fibrosis of the lung is rarely unilateral, unless it follows an old pleural effusion or symphysis of the pleura secondary to a long-continued pneumothorax which was complicated by a clear or purulent exudate, or indeed an old nontuberculous empyema. In the absence of a suggestive history the diagnosis of extensive unilateral fibrosis is not justifiable, and chronic massive atelectasis should be thought of. I know of many patients who lost the best opportunity to profit by an induced pneumothorax because of the physician's fear of striking pleural adhesions in cases of this type.

FIG. 1.[3] Roentgenogram showing an acute massive collapse of the right lung following haemoptysis. Note deviation of the trachea and mediastinal contents to the right.

FIG. 2. Roentgenogram taken 20 days later, showing clearing of the atelectasis on the right side.

FIG. 3. Roentgenogram showing a right upper lobar massive collapse following haemoptysis.

FIG. 4. Roentgenogram taken 6 days later, showing a clearing of the atelectasis.

FIG. 5. Roentgenogram showing chronic massive atelectasis on the left side. Patient's condition has been quiescent for over 3 years.

LOBULAR ATELECTASIS

The lobular or confluent lobular type of atelectasis in tuberculosis is the most prevalent, and the least appreciated. It may occur in any part of the pulmonary field, but the most favorable areas for its development are in the lower aspect of the upper lobes anteriorly, particularly on the right side. It is also often encountered in the retrocardiac area. In the latter position it is frequently mistaken for a nonspecific infection of the lower lobe, and in the former for an exudate at the upper right interlobular area, or indeed a pneumonic consolidation of tuberculous origin.

However, the clinical course in either case antagonizes the orthodox conception of the pathological process. In the case of the supposedly benign nontuberculous basal infection, the clinical course is active, as seen in most basal tuberculous lesions. On the other hand, in patients with the supposed tuberculous pneumonia of the upper lobe of the right

[3] Figs. 1, 2, 6 and 7 are reproduced with the kind permission of the Editor of the *Journal of the American Medical Association.*

FIG. 1

FIG. 2

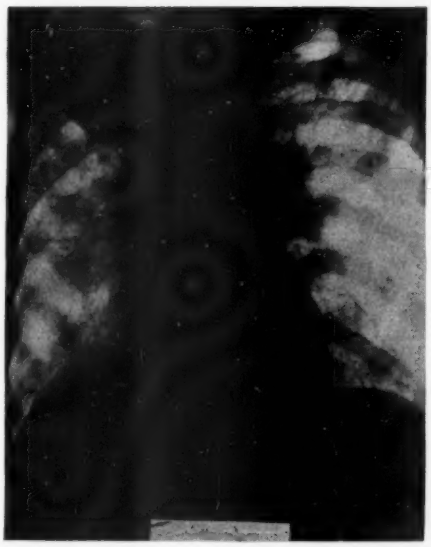

FIG. 3

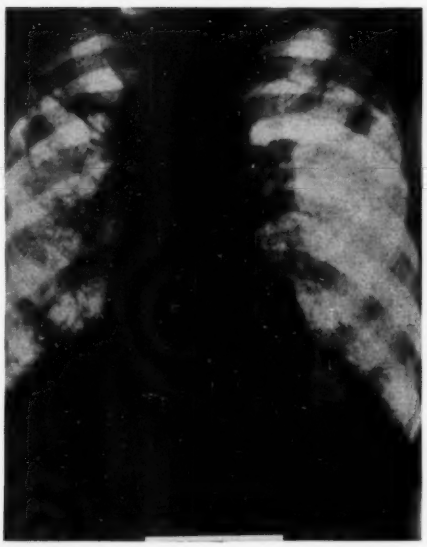

FIG. 4

FIG. 5

lung, the course is comparatively mild and, what is more striking, an induced pneumothorax often shows no evidence of an interlobar exudate or adhesions, and the density seen before inflation may vanish with great rapidity.

A study of chest roentgenograms of patients with limited lesions shows that the changes usually ascribed to fibrosis occur with much greater frequency than could be reasonably expected in view of the short clinical history. The changes referred to are (1) deviation of the trachea and mediastinal organs toward the involved side, (2) narrowing of the interspaces at the site of the lesion, and (3) elevation of the homolateral leaf of the diaphragm.

FIG. 6. Roentgenogram showing chronic massive atelectasis of the right lung. Note complete acquired dextrocardia and tracheal deviation to the right.

FIG. 7. Roentgenogram showing almost complete therapeutic pneumothorax with the heart and mediastinal contents in normal position and no evidence of extensive pleural changes. The right portion of the diaphragm is elevated because of a right phrenicectomy.

FIG. 8. Roentgenogram showing infiltration and tuberculous atelectasis at the base of the upper lobe of the right lung with possible exudate in the right upper interlobar area.

FIG. 9. Roentgenogram taken after induction of pneumothorax showing no evidence of exudate in the right upper interlobar area.

FIG. 10. Roentgenogram taken of a young man who has been ill but 2 months. Note early infiltration in the right upper lobe, narrowing of the right hemithorax and approximation of the ribs over the area involved.

Pratt and Bushnell (4) spoke of these changes as early signs of pulmonary disease, and Norris and Landis (5) found a decrease in the size of the hemithorax in unilateral incipient tuberculous lesions.

The extent of the mediastinal displacement in phthisis has for a long time misled physicians and roentgenologists in estimating the degree of pleuropulmonary fibrosis and thus adversely influenced the accuracy of their prognostications.

It was commonly assumed that when the mediastinal structures were pulled to the side of the lesion, it constituted sufficient evidence of healing to render the prognosis favorable. This concept is untenable in view of the recent realization that lobular and confluent lobular atelectases cause a deflection of the mediastinum toward the involved side. This is particularly true of the hilum structures which are definitely distorted and markedly pulled toward the atelectatic area, be it in the right or left upper lobe. This distortion and displacement vanish with the induction of artificial pneumothorax even though the intrapleural pressure remains

FIG. 6

FIG. 7

FIG. 8

FIG. 9

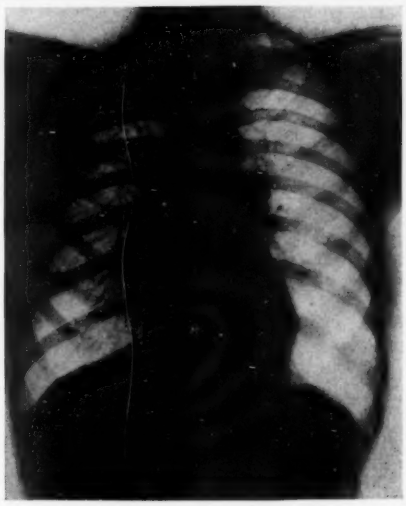

FIG. 10

FIG. 11

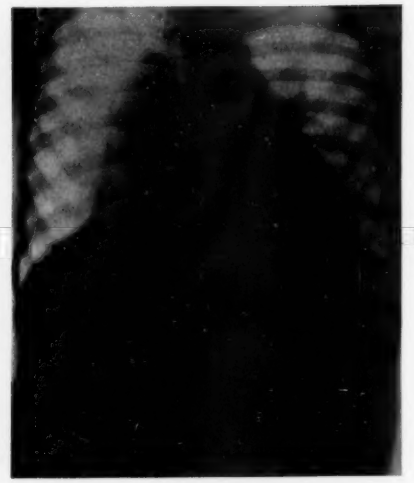

FIG. 12

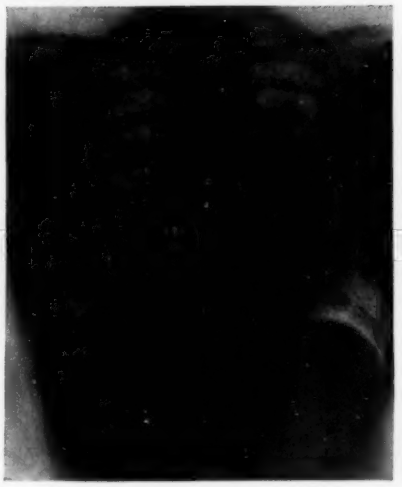

FIG. 13

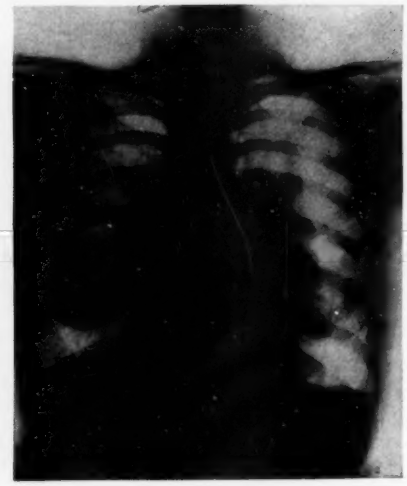

FIG. 14

FIG. 11. Roentgenogram showing recent but extensive infiltration and cavitation of the right upper in a girl of 7. Note marked hilum displacement to right.

FIG. 12. Roentgenogram showing no evidence of adhesions on the right following the induction of pneumothorax. Note collapse of cavity.

FIG. 13. Roentgenogram showing recent involvement of midportion of left upper. Note deviation of hilum structures to left.

FIG. 14. Roentgenogram taken after induction of pneumothorax. Note absence of adhesions and normal positions of mediastinal organs.

highly negative. Accordingly, far from being a sign of a favorable omen, the hilum displacement merely signifies recent tuberculous atelectasis which is to be treated as the clinical course of the disease demands.

The great frequency of lobular atelectasis would suggest that it is not of merely accidental occurrence in tuberculosis, but that it plays an important rôle in the involution of the tuberculous pulmonary processes.

It has been shown by Bruns (6) and Coryllos and Birnbaum (7) that the circulation is progressively impaired in the atelectatic lung, and that circulation in and ventilation of the lung are parallel functions. When ventilation is impaired, as in atelectasis, the circulation is decreased.

Leriche and Policard (8) and others have shown that fibrosis almost inevitably follows in areas deprived of an adequate oxygen supply or whenever local tissue respiratory deficiency occurs. Indeed there is ample clinical evidence to show that atelectasis in any lung area not only precedes and hastens fibrosis, but is also instrumental, by virtue of limiting local blood-supply, in materially diminishing toxic absorption.

More recently attention has been called to another important salutary effect of atelectasis in phthisis. It is well known that the tubercle bacillus is a strict aerobe and that virulent cultures consume three times as much oxygen as an equivalent weight of dog's muscle at rest. By depriving tubercle bacilli of their oxygen, they are markedly attenuated and may not grow on subculture (9). By creating a condition of anaerobiosis in the atelectatic area the growth of tubercle bacilli must necessarily be markedly impeded if not entirely abolished.

ATELECTASIS IN INDUCED PNEUMOTHORAX

Compression atelectasis is often observed in pneumothorax when the intrapleural pressure is maintained above zero in the absence of extensive adhesions. It can also be seen in any free pneumothorax when the intrapleural pressure is raised during a forced expiration. In either case, because of the patency of the bronchi, the atelectasis vanishes rapidly with the release of the positive intrapleural pressure.

It is different in the case of lobar or multilobar atelectasis secondary to bronchial obstruction in the course of pneumothorax. Here the process is more permanent and is often mistaken for a complicating tuberculous pneumonia, although the usual favorable clinical course antagonizes such an interpretation.

When lobar atelectasis occurs, the dense shadow representing the airless lung does not respond to respiratory efforts in spite of the negative intrapleural pressure. Moreover, the shrinkage in the volume of the lung creates a greater negative intrapleural pressure, with the result that the mediastinal contents are sharply drawn toward the side of the

pneumothorax. This, as can be readily seen, is due, not to the absorption of air from the pleura, for it occurs in spite of judiciously spaced refills, but to the absorption of the alveolar air distal to the plugged bronchi.

When Barlow and Kramer (10) first introduced the term "selective collapse" of the lung in tuberculosis, Hennel and Stivelman (11) showed that the providential collapse of the more involved portion was due to its diminished distensibility and elasticity, but it appears now that the rapid loss of distensibility of the involved portion of the lung is due not to fibrosis which is of slow evolution, but to lobular atelectasis, which is engendered with great rapidity and which precedes the more permanent fibrosis of the lung in cases treated with pneumothorax.

COLLAPSE OF CAVITIES

While pneumothorax is now extensively employed in the treatment of tuberculous lung processes even before cavity-formation, it is a fact, nevertheless, that in the vast majority of cases this procedure is employed in an effort to collapse cavities which are a constant and serious source of danger to the patient and the community.

It is a matter of common knowledge that induced pneumothorax can be applied either to compress the lung more or less forcibly or to permit the lung to collapse of its own accord after the potential pleural cavity has been converted into an actual air-pocket.

In the first instance the intrapleural tension is judiciously but steadily increased until, in the presence of a fixed mediastinum or propitiously placed adhesion, a high positive pressure can be safely created and maintained. In such cases compression of cavities often occurs to the great benefit of the patient.

On the other hand, the vast majority of successful pneumothoraces are of the low-pressure type, that is, the tension in the air-pocket created by separating the visceral from the parietal pleura is less than zero. How is it then that cavities in direct communication with the atmosphere are often collapsed, and healed under these negative pressures?

The answer to the question will be apparent if we recall that a tuberculous cavity is constantly and effectively drained and ventilated by the bronchi with which it communicates. It is this free communication with the atmosphere which helps to keep the cavity distended. Indeed, should there be a ball-valve mechanism permitting the ingress and interfering with the egress of air, the cavity may become larger and larger and ultimately rupture and cause a spontaneous pyopneumothorax.

FIG. 15

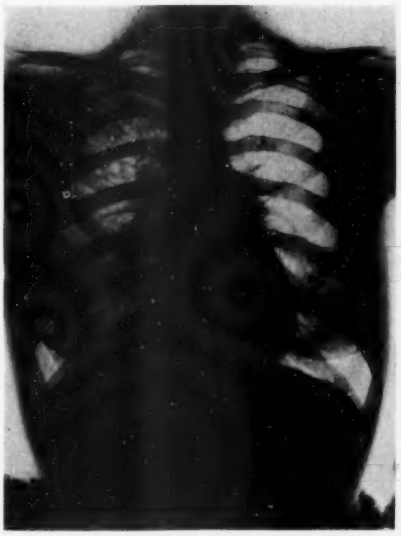

FIG. 16

FIG. 17

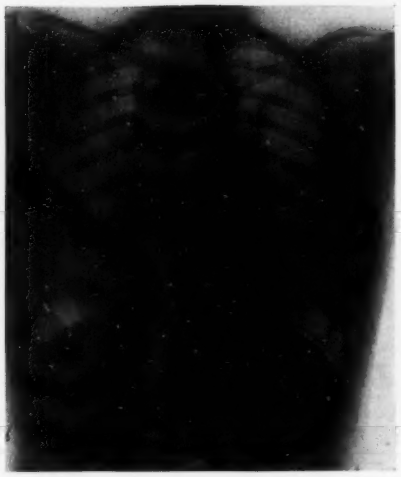

FIG. 18

FIG. 15. Roentgenogram showing extensive infiltration and multiple cavitation of right upper.

FIG. 16. Roentgenogram taken 3 months later showing complete obliteration of the cavities under negative-pressure pneumothorax.

FIG. 17. Roentgenogram showing huge cavity at the right apex with fluid-level. The lung is one-third collapsed by pneumothorax.

FIG. 18. Roentgenogram of same patient 3 months later showing complete obliteration of the cavity with pneumothorax maintained at negative pressures.

When pneumothorax is induced the lung shrinks from the periphery toward the hilum. In this process the position and the direction of the bronchi are inevitably affected. This is particularly true of the smaller bronchi which have no cartilagenous rings, and therefore lack the rigidity of the larger bronchi.

Postmortem studies show that in the vast majority of instances it is the soft smaller bronchi that ventilate and drain tuberculous cavities, and these may be so kinked by the change in the position of the lung in the course of pneumothorax as to be completely shut.

When this occurs the lung tissue and cavity it contains lose their means of ventilation, and the air distal to the point of obstruction is rapidly absorbed. This causes a complete local atelectasis. Further absorption of the air from the cavity results in the creation of a high negative pressure within it which can be compensated only by the approximation of its walls. When this is accomplished healing of the cavity continues uninterruptedly if the pneumothorax refills are judiciously maintained.

SUMMARY

1. Acute massive atelectasis is rarely observed in pulmonary tuberculosis, but it may occur when a large bronchus is plugged as a result of haemoptysis.

2. Chronic massive atelectasis in phthisis is most often confused with extensive unilateral pleuropulmonary fibrosis. Patients so affected may run a benign course, but, when dyspnoea develops as a result of extensive mediastinal deflection, they can be effectively treated with artificial pneumothorax.

3. Confluent lobular atelectasis occurs very frequently and early in the course of phthisis. It encourages local fibrosis by producing a local tissue respiratory deficiency.

4. Tubercle bacilli being strict aerobes are markedly attenuated when they are deprived of an adequate amount of oxygen. Lobular atelectasis by impairing the local circulation materially diminishes the available oxygen supply in the area involved, and so adversely affects the growth of the tubercle bacilli.

5. All forms of atelectasis are to be seen in lungs treated with artificial pneumothorax. This accounts for the rapid fibrosis of lesions under collapse therapy.

6. The collapse of cavities in negative-pressure pneumothoraces is

brought about by the absorption of the air they contain following the kinking of their draining bronchi. The high negative pressure thus created within them forces an approximation of their walls. When this is accomplished healing of the cavity may continue uninterruptedly if further collapse is judiciously maintained.

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ABDOMINAL CONDITIONS INFLUENCING THE LUNGS AND PLEURAL PRESSURE IN PULMONARY TUBERCULOSIS[1,2]

BURGESS GORDON

It is recognized that artificial pneumothorax, phrenicectomy and thoracoplasty influence favorably the course of selected cases of pulmonary tuberculosis. This is attributed to the effects of limitation of motion of the diseased lung. It has been observed also, that an extension of the tuberculous process occurs when artificial-pneumothorax treatments are stopped prematurely. In tuberculous pregnant women a similar picture has been noted. During the later months of pregnancy the pulmonary process seems in abeyance, but after delivery there is a striking increase in signs and symptoms. Quiescence has been attributed to an increase in general metabolism, and reactivity following delivery as the result of the strain of labor, disturbed metabolism, lactation and sepsis (1). The variations in the level of the diaphragm have been considered recently as a possible factor (2). It has been suggested in this hypothesis that compression of the lungs, especially from below upward, and alterations in the pulmonary circulation develop increasingly during the last four months of pregnancy. These may play a part in quiescence. It is possible that the reappearance of symptoms after delivery is due in part to the abrupt lowering of the diaphragm, a mechanism comparable to that when the diaphragm returns to a normal level following regeneration of the phrenic nerve.

Other conditions suggest a relationship between the elevation of the diaphragm and the degree of activity of pulmonary tuberculosis. In individuals with relaxed abdominal wall and viscera in a state of ptosis the downward movements of the lungs are exaggerated. The "abdominal" type of breathing almost entirely replaces true "thoracic" breathing.

[1] From the Medical Service of Dr. Thomas McCrae and the Department for Diseases of the Chest, Jefferson Hospital, Philadelphia, and the White Haven Sanatorium, White Haven, Pennsylvania.

[2] Read at the annual meeting of the Association of American Physicians, Washington, D. C., May 11, 1933.

This is striking in multiparous women after delivery and in all individuals who were formerly obese. The influence of certain types of general physical development may be considered also as a factor in the progression

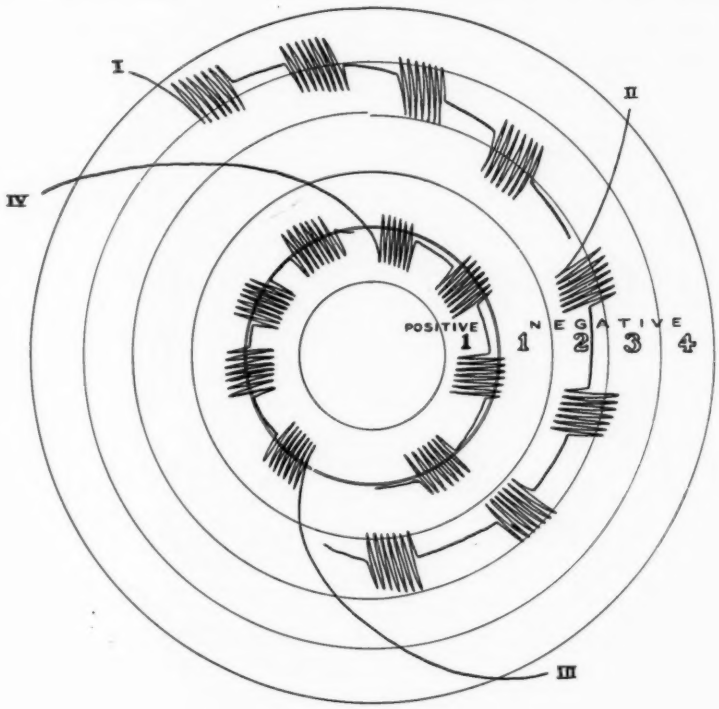

FIG. 1

A composite drawing from a series of tracings of artificial-pneumothorax pressures is shown in this figure (case 1). The numerals in the circular spaces represent the degrees of pressure. Each space to the right of the fine double circles indicates negative pressure (one space is equivalent to a pressure of 2 cm. of water). The space to the left of the double circles, indicated by heavy numeral I, is the positive zone. Graph 1, made during the second month of pregnancy, shows the variations in pleural pressure (negative) during the excursions of the lungs after each injection of air into the pleural cavity (total air injected is 750 cc.). Graph 2 shows the curves during the 4th month of pregnancy (total air injected 650 cc.). The straight lines following each series of excursions designate the periods when air was injected into the pleural cavity. It is noted that as the amount of air in the pleural cavity increases the graph approaches the neutral zone (fine double circles). Graphs 3 and 4 were made during the 6th and 7th months of pregnancy and indicate that positive pressure existed without the injection of air into the pleural cavity (the result of the progressive elevation of the diaphragm).

of pulmonary tuberculosis. Since the earliest times the long type of chest and long thin abdomen have been associated unfavorably with the

course of pulmonary tuberculosis, whereas the rounded or athletic type of chest, and the obese and well-developed abdomen have suggested greater resistance. There may be a similar relationship between an enlarged liver with ascites and the abeyance of far-advanced pulmonary tuberculosis. It is striking in some cases that toxic manifestations and respiratory symptoms become less pronounced and life continues

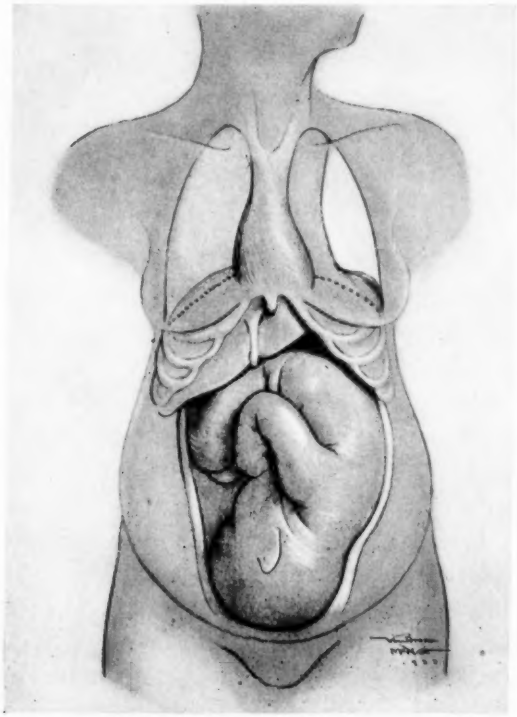

FIG. 2

(Case 1.) This shows pregnancy at the eighth month, pneumothorax (left lung), shift of the heart to the right and elevation of the diaphragm (greater on the left side). The dotted line represents the level of the diaphragm during the first month of pregnancy.

longer than would be expected in patients with uncomplicated pulmonary tuberculosis.

These observations and impressions have aroused interest in the possible important relationship of the abdominal wall, the abdomen and its contents to the course of disease in the lungs. During the past two years the events in tuberculous patients with pregnancy or abdominal tumors,

ascites and enlarged liver have been followed. Objective data have been obtained by anatomical measurements of the chest, roentgenograms, fluoroscopy, estimations of the intrathoracic pressure (3) and a tabulation of clinical signs and symptoms. The following cases are reported:

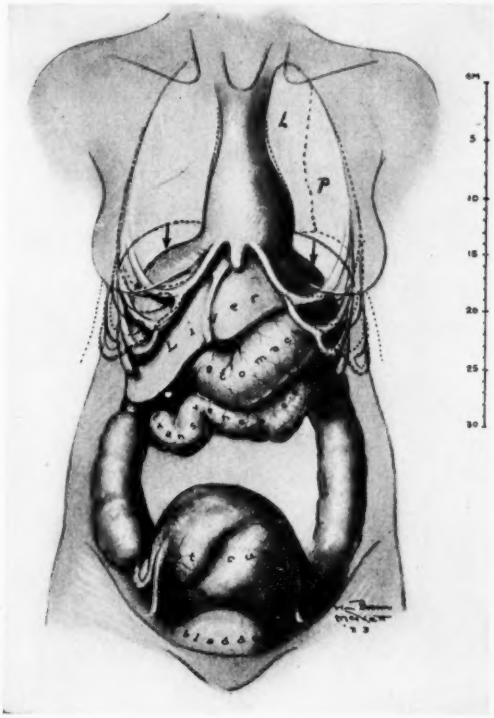

FIG. 3

(Case 1.) The area designated by "L" is the collapsed lung; space "P" is the pneumothorax; the dotted line forming the base of this triangle indicates approximately the highest level of the diaphragm during pregnancy; the line below is the level at the fifth month. The lowered diaphragm and visceral contents indicate the probable position of the organs after delivery comparable with so-called "visceroptosis." The lateral dotted lines show the relative dimensions of the thorax during pregnancy.

1: H. F. (Hosp. no. V-C-459), female, age 27, was admitted to the Department for Diseases of the Chest, Jefferson Hospital, with diagnosis of far-advanced tuberculosis of left lung, moderately advanced change in apex of right lung and pregnancy of one-month duration. Artificial pneumothorax had been instituted on left side about one year before entry. During first four months in Hospital there were no striking variations from normal in left lung, but râles and alterations in breathing continued at right apex. Cough and expectora-

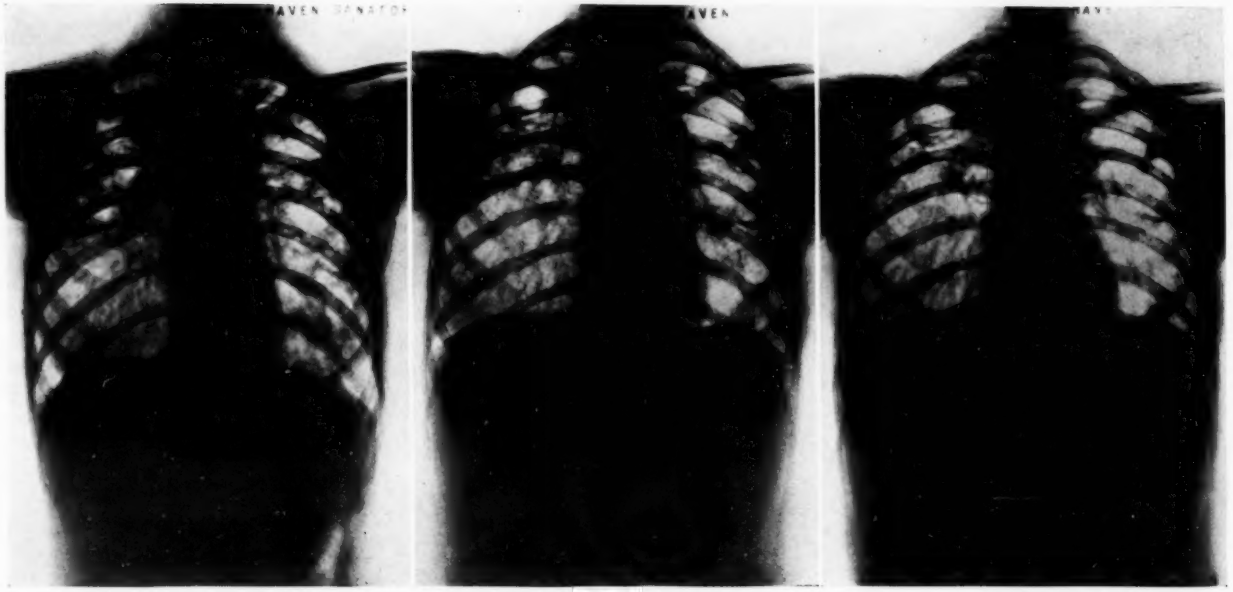

FIG. 4

This shows differences in elevation of the diaphragm and density of the lung fields. Roentgenogram on left was taken (Dr. R. K. Childerhose) on February 2, 1932, before abdominal changes were noted. Roentgenogram in centre (Dr. R. K. Childerhose), on August 21, 1932, shows an elevation of the diaphragm. Roentgenogram on right (Dr. L. P. Anderson), was taken on April 16, 1933, after marked ascites and enlarged liver had occurred. In this, as compared with the left, a striking elevation of the diaphragm and clearing of the lung fields are noted. With the elevation of the diaphragm a corresponding improvement in pulmonary signs and symptoms is also noted. The patient is now suffering chiefly from the abdominal condition.

tion were moderate. The afternoon temperature varied up to 99.4°. Since the collapse of the left lung had been effective and there was no considerable progression in the right lung, artificial-pneumothorax treatments were continued on the left side. A negative pleural pressure equivalent to 1–2 cm. of water was maintained. During fifth month of pregnancy fluoroscopic examination by Dr. John T. Farrell, Jr. showed elevation of left diaphragm.

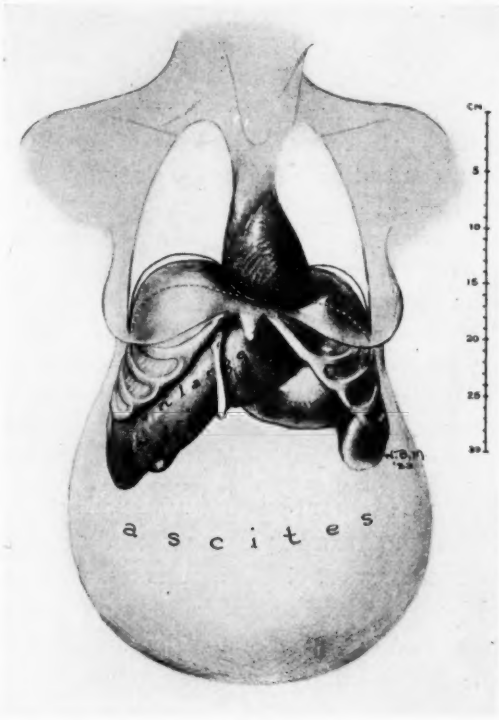

FIG. 5

(Case 2.) This shows a massive ascites and enlarged liver. The lower dotted lines indicate the level of the diaphragm on the patient's entry to the hospital. The curved lines above show the highest excursions of the diaphragm after the occurrence of ascites and enlarged liver.

The total increase during the 6th month was about 2.5 cm. Coincident with this elevation there was an increase in intrapleural pressure (figure 1), as evidenced first by pain in left chest. Fluoroscopic examination of chest showed heart shifted about 1.5 cm. to right side. Artificial-pneumothorax treatments were discontinued. Pain in chest persisted for two weeks, and it was necessary to remove air on three occasions (total 850 cc.). During seventh month of

pregnancy there was further elevation of diaphragm on left side, and total increase of 2 cm. in right side. The pleural pressure on the left side varied between minus 1 and plus 1. A pleural effusion (left side) developed during eighth month, and further pressure determinations and fluoroscopic studies of diaphragm elevations were not made. The transverse diameter of the lower thorax at end of eighth month showed a total increase of about 3 cm. The signs over the right apex suggested clearing; cough and expectoration decreased. The temperature was normal. The events are shown in figures 1, 2 and 3.

2: M. S. (Hosp. no. 5,857), female, age 32, was admitted to White Haven Sanatorium January 5, 1932, with diagnosis of far-advanced pulmonary tuberculosis, with onset about two years before entry. Temperature elevation varied between 99° and 101°, and expectoration between 90 and 150 cc. daily. During sixth month after entry fulness of abdomen was noted. Increasing enlargement of liver and ascites occurred during fall of 1932 and winter of 1933. In March, 1933, the liver was palpable about one hand-breadth below costal margin. There was striking decrease in pulmonary signs and symptoms. The roentgenograms of the lungs (figure 4) and physical measurements (figure 5) showed that with enlargement of liver and ascites there was progressive elevation of the diaphragm. A marked decrease in the pulmonary cavities occurred.

It appears from these observations that the level and movements of the diaphragm are influenced definitely by a mass in the abdomen and a rise in the intraäbdominal pressure. The force exerted upward, that is, against the diaphragm, is noted in graphs showing an increase in pleural pressure. It seems that elevation of the diaphragm in these conditions is comparable with that in bilateral phrenicectomy.

The mechanism of diaphragmatic elevation resulting from increased abdominal pressure may have an important clinical application in the management of pulmonary tuberculosis. Evidently, abdominal tumors cannot be produced, and pregnancy may not be advisable but, if present, may be utilized to advantage. The mechanism may be useful, especially in the management of lesions in the left lung, because on this side the possibility of diaphragmatic elevation is greater (mobility of the stomach is apparently a factor). However, the most important consideration of the mechanism may be in the after-treatment of pregnant women, following the removal of large abdominal tumors and in patients who have had extreme and rapid loss of weight. Since an abrupt lowering of the diaphragm may convert an essentially "thoracic" type of breathing into

an "abdominal" type, resulting in deep excursions of the lungs and consequent spread of disease, it would seem that measures should be taken to counteract the reduced diaphragmatic support. These may be considered as follows: Elevation of the foot of the bed causing the viscera to shift toward the upper abdomen, the use of a binder with a concave metal (abdominal) surface to compress the abdominal wall, the induction of collapse of the lung by artificial pneumothorax or phrenicectomy, the use of a special abdominal support (4) after the patient begins exercise, and increasing considerably the body weight.

CONCLUSIONS

1. The study shows that a progressive elevation of the diaphragm occurs with an increase in the size of abdominal contents. The elevation of the diaphragm may reach a higher level on the left than on the right side.

2. With elevation of the diaphragm there is a decrease in the vertical excursion of the lungs.

3. The favorable pulmonary events in a case of far-advanced tuberculosis of the lungs with pregnancy and a tuberculous patient with ascites and enlarged liver suggest a picture not unlike that seen in phrenicectomy.

4. The mechanism of diaphragmatic elevation in pregnancy may be considered as a possible factor explaining the abeyance of pulmonary tuberculosis. The abrupt lowering of the diaphragm after pregnancy may be considered as one of the factors explaining the spread of infection.

5. Various measures to favor the elevation of the diaphragm are suggested.

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AMBULATORY ARTIFICIAL PNEUMOTHORAX IN THE TREATMENT OF TUBERCULOSIS IN THE NEGRO[1]

J. W. CUTLER, W. H. RODGERS AND I. B. CIPPES

The following study is reported to show what the tuberculosis clinic can do, by means of collapse therapy, for Negro patients when sanatorium treatment is unavailable or long delayed.

It is well known that tuberculosis is about four times as prevalent in the Negro as in the white man, and in the Negro more often runs a rapidly fatal course. In Philadelphia during 1932 there were 508 recorded deaths from tuberculosis of the lungs out of a Negro population of 241–574, as against 889 deaths out of a white population of 1,737,305, or a death rate of 210.3 compared with 51.2 per 100,000 population. Estimated on the basis of nine cases for each recorded death, there were in addition 4,572 cases of pulmonary tuberculosis among Philadelphia Negroes needing treatment during that year. To accommodate some such number, there are 128 beds. This estimate is based upon the number of colored patients with tuberculosis actually hospitalized on November 15, 1933, in the various institutions in and near the city admitting them, and in State sanatoria in which beds are set aside for Philadelphians. Thus only one out of every 35 Negro patients in need of treatment has a chance for hospitalization. As for the rest, they must remain at home, many without adequate treatment, some with none at all. It is a common experience at the Phipps Institute that from six months to a year elapses from the time the patient is placed on a sanatorium waiting-list until he is admitted.

It is evident that the control of tuberculosis in the Negro is a major problem in public health. In the United States there are about twelve million Negroes, of whom about 226,000 are in need of hospitalization for tuberculosis. If conditions in Philadelphia are typical of the rest of the country only 3 per cent of this total are cared for in institutions at any one time. Since colored people with tuberculosis are sources of contagion not only to their own families and race, but also under certain condi-

[1] From The Henry Phipps Institute of the University of Pennsylvania, Philadelphia, Pennsylvania.

tions to members of the white race, tuberculosis in the Negro is clearly the white man's problem from every point of view.

PLAN OF TREATMENT

It has seemed to us that a solution to the question of long waiting-lists lies in the wider and earlier application of modern surgical treatment, particularly artificial pneumothorax. Rest is the prime essential in the cure of tuberculosis, valuable as fresh air, diet and sanatorium regimen may be. Collapse therapy gives to the diseased lung the most complete form of rest possible, and so produces its results in the shortest possible time. Furthermore it can be carried out in local institutions within a few days after a diagnosis has been established.

For the past two and a half years this conviction has been put to a clinical trial at The Henry Phipps Institute, through the kindness of Dr. H. R. M. Landis. Through his interest a clinic was established in May, 1931, for the ambulatory treatment of both white and colored patients suitable for artificial pneumothorax who were unable to obtain immediate sanatorium care. The present paper deals with the Negro patients treated. The method used as applied to about 100 white patients and a few colored patients between November, 1929, and the spring of 1933 has been described by one of us (1).

The general plan was to select certain patients attending the clinic of the Institute who had been diagnosed as tuberculous, and to establish the pulmonary collapse in a local hospital. A short period of hospitalization, one week if possible, was to be followed by treatment at home, the patient reporting to the Out-patient Pneumothorax Clinic for refills at stated intervals. The course of the illness was to be repeatedly checked by fluoroscopic and X-ray studies and by the blood-sedimentation rate. At first the patient was to remain in bed between clinic visits, and then to undertake graduated exercise as the indications warranted. We applied the term *ambulatory pneumothorax* to this scheme of treatment.

Our greatest difficulty was to persuade general hospitals to assign beds in their wards for patients with tuberculosis, and in particular for Negro patients. More recently, through the kind efforts of Dr. Minton, the Board of the Mercy Hospital assigned one bed, so that the plan could be given a fair trial. With the exception of an occasional bed in other institutions, this is the only one available to us for the immediate hospitalization of Negro patients. That we are now able to report even as

many as 37 cases under these conditions, suggests what can be done with existing facilities. Moreover, further experience has convinced us that although temporary hospitalization is highly desirable it is not always indispensable. Not infrequently the initial inflation can be given in the outpatient clinic with safety, if the quantity of air injected is small, and if the patient rests for a few hours after treatment.

During the early part of our study we tried as far as possible to select only the ideal case for artificial pneumothorax, that is, the patient with strictly unilateral involvement. As time went on we were encouraged by our results to recognize wider indications for collapse therapy. We have now definitely adopted ambulatory pneumothorax as a preferred form of treatment for colored tuberculous patients, to be instituted whenever we have a reasonable chance for success without undue risk. In this way we strive to place under treatment as large a number of patients as possible as soon as a diagnosis is established. When bed-space is finally available in a sanatorium, the more advanced cases are admitted and the treatment continued there.

Out of the total number treated in the ambulatory-pneumothorax clinic in the manner described, 37 were adult Negroes. They have made 768 visits and have been given 464 treatments. Although the number of patients is small, our results are so gratifying, and the means by which they were attained are so readily at hand, that we feel justified in calling attention to our procedure. It suggests a method by which clinics might make a concerted attack upon the problem of tuberculosis in the Negro, using existing facilities more effectively for the application of proved forms of treatment.

RESULTS OF TREATMENT

Table 1 briefly summarizes the condition before treatment and the present condition of these Negro patients, as shown by physical, roentgenological and laboratory observations. It will be noted that cavity-formation could be demonstrated either by physical signs or by X-ray in 32, or 87 per cent. In 13, or every third case, there was demonstrable disease in both lungs.

It will be observed that these cases are arranged in the order of their severity before treatment was instituted, those with the most favorable prognosis first. It is evident that among the groups that had appeared clinically the most promising are found the largest number of patients improved and at work as the result of treatment. For the most part

they were the "good unilateral cases," those that are ideal for ambulatory pneumothorax. These, instead of having to wait for sanatorium admission in order to obtain treatment, were taken in hand while the disease was in a tractable stage. Many such cases can be returned to work in a short time, with their sputum made harmless, through collapse therapy without sanatorium care.

When more widespread destruction of the lung has occurred, the results are less dramatic. However it is our opinion that many patients are helped by this treatment who would undoubtedly be much further

TABLE 1

Results obtained in adult Negro tuberculous patients treated by ambulatory pneumothorax

Classification based upon clinical, X-ray and laboratory findings

TYPE OF CASE TREATED	NUMBER OF CASES	WORKING: SPUTUM NEGATIVE	IMPROVED: SPUTUM NEGATIVE	IMPROVED: SPUTUM POSITIVE	UNIMPROVED	WORSE	DEAD	POOR SPACE: TREATMENT STOPPED
Unilateral progressive. No cavity. Sputum negative....	5	2	3	—	—	—	—	—
Unilateral progressive. Cavity. Sputum negative.....	9	4	3	—	1	—	1	—
Bilateral tuberculosis. Cavity. Sputum negative.....	1	—	1	—	—	—	—	—
Unilateral tuberculosis. Cavity. Sputum positive.....	10	1	1	5	—	—	—	3
Bilateral tuberculosis. Cavity. Sputum positive.....	12	1	—	3	1	1	2	4
Total.....	37	8	8	8	2	1	3	7*

* Of these 4 are dead.

advanced, some of them dead, by the time that sanatorium care is available. As it is, the results compare favorably with those obtained in similar periods of time in sanatoria handling similarly advanced cases. As bed facilities become available we encourage these patients to accept sanatorium treatment. The scheme has been consistently employed solely to make use of the time elapsing between diagnosis and hospitalization.

It may be seen from the table that of 7 patients in whom satisfactory collapse could not be established because of extensive adhesions, four are now dead, although they were hospitalized soon after the diagnosis was made.

DISCUSSION OF CASES

The two case histories that follow have been selected from those that show clinical and anatomical arrest of advanced tuberculosis in Negro patients.

W. I., colored, male, age 24, was diagnosed as tuberculous with positive sputum on May 27, 1932. At that time there were fever, cough, expectoration with blood-streaked sputum, hoarseness, and loss of weight and strength. Occasional râles could be detected in the right upper lobe, and X-ray study revealed dense, close-set, flocculent spots above the posterior level of the sixth interspace on the right, with multiple small cavities within this area. The left lung was apparently normal. The patient was hospitalized for seven days (June 7 to 14, 1932), and a satisfactory therapeutic pneumothorax was established. He was then given instructions as to how to live at home and was ordered to report to the clinic at regular intervals for refills. He promptly regained excellent health and has maintained it to this day; he is self-supporting. The sputum is repeatedly negative. The tuberculous lesion has cleared so that only a few strands are visible in the X-ray film. The left lung has remained free from disease. At the present time the patient is given a refill every three weeks.

J. B., colored, male, age 39, was diagnosed as tuberculous on November 12, 1931. At that time there was consolidation involving the right upper lobe with a small cavity; râles were heard; and there was a scant infiltration of the left apex. The patient complained of cough, fatigue, and other symptoms of toxaemia. Pneumothorax treatment was instituted on November 28, 1931. The patient was hospitalized for a period of twelve days, and then permitted to return to work, as his general condition was good. He has been self-supporting as a janitor since that time, and is given a refill once in three weeks. Recent X-ray study shows only a strand-like formation of the right upper lobe, indicating a healed lesion. The infiltration and cavity-formation have disappeared.

Both of these cases illustrate the great economic value of therapeutic pneumothorax to tuberculous patients who cannot afford long absences from work. It is noteworthy, moreover, that when a satisfactory collapse is established in unilateral disease, the sputum promptly becomes free from tubercle bacilli. The colored patient especially who is waiting sanatorium admission is likely to be a prolific source of contagion to his associates. A study at the Phipps Institute showed that tubercle bacilli are recovered more often from dust in the homes and on the clothing of

colored than of white patients (2). More recently it has been shown by means of the Gaffky count that conspicuously larger quantities of tubercle bacilli are expelled in the sputum of Negroes (3) (4). Ambulatory pneumothorax is the treatment that best meets the urgent financial needs of many patients, enabling them to work without prejudice to their own physical welfare, and without exposing their families, their employers, or their fellow-workers to contagion.

It was of course particularly encouraging to us to obtain good results in severe cases. We found, however, that to be most effective collapse therapy should be applied even earlier to the Negro than to the white man, and, if possible, before excavation has occurred and before tubercle bacilli have appeared in the sputum, because of the tendency of the disease in the colored patient to run a more rapid and deadlier course than in the white. This was brought home to us at the beginning of our study, when, because of the lack of beds, only a small percentage of the Negro patients selected could be placed immediately under treatment. In a number who had to wait for some months, the lesions had become so extensive by the time a bed was secured that nothing could be done for them. What had been an early case only a short time ago was now a widespread, bilateral tuberculosis with unfavorable prognosis. We now seek to institute collapse therapy in minimal cases when there is X-ray evidence that the lesion is progressing or likely to progress.

The following case is particularly instructive.

M. G., female, age 21 years, was first seen in the pneumothorax clinic on June 15, 1931, when a diagnosis was made of minimal tuberculosis involving the upper third of the right upper lobe. There were no râles, and the sputum was negative for tubercle bacilli. Her general condition was good and her weight 143 pounds. By August, 1931, the sputum was repeatedly positive for tubercle bacilli, and râles could be heard in the right upper lobe. Artificial pneumothorax was advised but no bed facilities were available. By September, 1931, the entire right lung was involved with multiple cavities scattered throughout, and there was a lesion in the middle lung field on the opposite side. The patient was now too ill clinically, and the lesions too extensive, for ambulatory pneumothorax. She was admitted to one of the state sanatoria on December 8, 1931, and died there on February 10, 1932.

Within a period of less than three months the clinical picture changed from a minimal case with good prognosis to a far-advanced, bilateral, hopeless case.

Such instances have persuaded us that we should begin collapse therapy in colored patients as early as possible. They show convincingly what time lost while the patient is "on the waiting list" means in tuberculosis, particularly as it occurs in Negroes.

PRACTICABILITY OF THE PLAN OF TREATMENT

It may be noted that we have found ambulatory pneumothorax a thoroughly practicable form of treatment with our colored patients, who have been extremely coöperative throughout. During the entire two and a half years we have had but one patient who, refusing to coöperate, largely through ignorance, has dropped out from the clinic. The rest have kept all appointments, and in many respects have carried out instructions even better than our white patients. We believe our success is due to two factors. First, we have taken great pains to explain to the patient what the treatment is and what we hope to accomplish. We have warned him that the treatment is a prolonged one, that cure can come only after much persistent effort, and that the doctor cannot succeed without the constant aid of the patient.

A second factor in our success is the employment at the Institute of Negro nurses and Negro physicians to deal directly with the Negro patients. This plan has been described by Dr. Landis (5) (6), and its advantages have been urged by him for years. The Negro naturally feels more at home and has more confidence when treated by members of his own race. Moreover one of the important steps in the control of tuberculosis is, doubtless, to make the Negro race-conscious of its own responsibilities and of its own capabilities.

It is estimated that it might be possible to care for 50 per cent or more of the Negro tuberculous population in the United States in the manner described, in addition to the 3 per cent or less that are now hospitalized. The scheme of treatment appears to be rational and practicable. It makes possible a prompter application of a proved method of treatment, and a wider and more effective use of existing agencies, thus extending the function of the clinic as coördinator of all the facilities at hand for the control of tuberculosis.

SUMMARY

"Ambulatory pneumothorax" has been applied to a group of colored patients while they were awaiting admission to sanatoria. In most of the early cases, the disease was arrested and the patient at work within

from one to three months; some advanced cases were arrested; some others improved and continued the treatment in sanatoria when beds were available.

Only a short period of local hospitalization (one or two weeks) was required to establish the collapse, the patient thereafter coming to the pneumothorax clinic for refills. The scheme was found to have the following advantages, particularly as regards colored patients.

1. The lung is put to rest as soon as the diagnosis is made. Delayed treatment is especially disastrous in Negroes; we have seen minimal cases become far advanced within a few months, ending in death. We now apply ambulatory pneumothorax as a preferred form of treatment to our Negro patients, and institute collapse in them as early as possible.

2. The patient is usually able to return to full-time work soon after treatment is begun.

3. The sputum becomes free of tubercle bacilli with successful collapse in unilateral disease.

4. A wider use is made of existing hospital facilities for the application of proved methods of treatment. There are approximately 226,000 Negroes in the United States who need hospitalization for tuberculosis, with institutional facilities for about 3 per cent. It might be possible to care for 50 per cent or more by the method described, which we have found thoroughly practicable with our Negro patients.

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AIR-EMBOLISM COMPLICATING ARTIFICIAL PNEUMOTHORAX[1]

A Case with Autopsy

T. McCURDY

In the past few years there has been a trend toward surgical procedures in the treatment of pulmonary tuberculosis. Of these the most widely used is artificial pneumothorax, a relatively simple operation and adaptable to the use of any operator after some practice and a thorough understanding of the technique and the use of the necessary instruments.

Unfortunately, however, there are a few complications to be anticipated, of which the least common but the most dreaded is air-embolism.

Bruns (1) reports 13 cases of air-embolism with 4 deaths, occurring over a period of nine years, in approximately 12,700 pneumothorax operations, an occurrence of about 0.1 per cent, and a mortality among these of 30 per cent. Andrews (2) reports two probable instances in over 8,000 punctures, with one death. All these patients had pleural adhesions, which obviously increases the danger. The possibility of piercing the lung becomes more imminent; when it is once pierced, whether or not air is introduced from the needle, the danger is increased. In eight of the above-mentioned cases of Bruns, insufflation had not been started and in three no symptoms occurred until after the needle was removed. Apparently then, a communication established between a pulmonary vein and bronchus is quite sufficient to produce air-embolism.

"Pleural shock" has commonly been blamed for most of the sudden deaths occurring during operations on the chest. It presents a syndrome identical to that seen in air-embolism with cardiorespiratory embarrassment, clonic and tonic muscular spasms, loss of consciousness and sometimes death. The mechanism has never been proved, but reflex action between the pleura and pulmonary circulation is Meakins's hypothesis (3).

The above-cited clinical experiences would tend to make one doubt the rôle of pleural shock as the cause, when these sudden and severe

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symptoms arise during chest surgery, and to stimulate a more thorough search for evidence of air-embolism in these patients (4).

The following case illustrates clinical and autopsy findings in air-embolism:

Clinical: A white male, 31 years, was admitted with advanced bilateral pulmonary tuberculosis and cavitation. Twenty-three insufflations of from 50 to 500 cc. of air were done on the right side during the next six months, with only partial collapse. Then six injections were made into the left chest, with resulting slight collapse in the lower chest cavity. The final injection, which is the basis for this report, was made in the second right intercostal

FIG. 1. PHOTOGRAPH OF RIGHT LUNG SHOWING NEEDLE-HOLE IN VEIN-WALL

space, midclavicular line. The initial manometer reading was −40, −35, approximately the same as former initial readings on this side. After the introduction of 200 cc. of air, the patient complained of feeling sick and began to move about on the table. The needle was removed immediately. The face and hands became cyanotic, and there was marked air-hunger. The pupils were widely dilated. Caffeine-sodium-benzoate was given subcutaneously, together with adrenalin into the heart-muscle, but the patient responded to neither and expired in about one minute. An immediate examination of the eye grounds showed air-bubbles in the retinal vessels.

Anatomical diagnosis (T. M.): Air-embolism, with a large amount of air in the right atrium and ventricle; numerous air-bubbles throughout the cerebral vessels and inferior vena cava; bilateral diffuse fibrosing pulmonary tuberculosis, with multiple cavities in the left apex; pleuritis, obliterative, over entire right lung and upper lobe of the left; partial collapse of the lower lobe of left lung due to artificial pneumothorax; needle-puncture wound in the second interspace of the right anterior chest, extending through adherent parietal and visceral pleurae into a pulmonary vein, with moderate haemorrhage into the intercostal muscles and adjacent lung tissue.

Necropsy: "The right pleural cavity is found to be entirely obliterated by fibrous adhesions, which necessitates removing the lung with parietal pleura attached. The track of a recent needle-puncture extends 2.5 cm. into the lung. There is a zone of haemorrhage, 1.5 cm. thick, around this track. There is a needle-puncture hole leading into a distended medium-sized pulmonary vein at the end of the track. The right side of the heart is considerably dilated with dark red and extremely frothy blood. . . . The vessels over the convex surface of the cerebri are widely distended with blood and contain numerous large air-bubbles. The inferior vena cava also contains many large air-bubbles."

Microscopic: Sections examined from all organs confirm the anatomical diagnosis.

DISCUSSION

Because of the large amount of air found in the right heart and systemic vessels, it is logical to suppose that the entire 200 cc. was injected into the vein. The initial negative manometer reading would support such a finding. The patient had no remaining pleural cavity, and such a reading could only come from the normal negative pressure within the pulmonary veins, increased by parenchymal pathological changes (5). The air, injected very slowly, apparently passed through the left heart without causing symptoms. A large part traversed the systemic system and returned to the right heart, where the formation of an elastic air-cushion stopped the circulation. No air was found in the pulmonary arteries

COMMENT

On entering the pleural cavity, there is always danger of sudden and severe symptoms arising, which may result in death. When these deaths occur it is important that autopsies be done to prove the presence

of air-embolism, and rule out pleural shock. Autopsies should be done soon after death, as putrefaction begins early, sometimes with the production of gas. Care should be taken, in opening large vessels, that air is not admitted from the outside. Organs may be opened under water to aid in recognizing small amounts of air.

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TUBERCULOUS BACILLURIA

An Experimental Study with Acid-Fast Bacteria of Low Pathogenicity[1]

LALL G. MONTGOMERY[2] AND RAYMOND B. ALLEN[2]

Since bacteria are often present in the urine, Cohnheim (1882) advanced the hypothesis that the kidneys helped to rid the body of these invaders by simple excretion. He believed, accordingly, that tubercle bacilli found in the urine of a person whose urinary tract was free from lesions of tuberculosis must have been excreted and derived from a tuberculous focus elsewhere in the body and excreted by uninjured kidneys.

Wyssokowitsch's (1886) original investigation, in which rabbits were used as experimental animals, laid the foundation of knowledge on this subject. Twelve species of bacteria which do not commonly cause lesions in the kidney were used in 27 experiments. Samples of urine were obtained aseptically from the bladder at necropsy at various intervals after intravenous inoculation, and Wyssokowitsch was unable to find bacteria in a single specimen by staining and culture. However, in 13 of 17 experiments with bacteria which frequently cause renal lesions (cocci and colon bacilli, but not the tubercle bacillus) organisms were recovered from the urine, but only after at least two hours had elapsed following inoculation. Wyssokowitsch concluded that the passage of bacteria into urine occurs only when blood containing them escapes through some break in the secretory membrane, caused by mechanical or inflammatory injury. This conclusion has been fully corroborated by many subsequent investigators, notably Pernice and Scagliosi, Sherrington, Lepper, Dyke, Lieberthal and Von Huth, and recently by Helmholz (6) (7), who has made exhaustive studies.

A clearly contradictory result was obtained by Biedl and Kraus, who reported that organisms appeared in the urine within five minutes after injection. Their work, however, has been generally discredited because the urine was collected from cut ureters by means of cannulas, thus permitting contamination by blood.

[1] Work done under the direction of Doctor W. H. Feldman.

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Notwithstanding the experimental evidence against such a hypothesis as that of Cohnheim, the belief in excretory bacilluria persists and recurs frequently, particularly in the literature on urology. This is doubtless due to the fact that occasionally a surgeon has the embarrassing experience of removing a kidney suspected of being tuberculous (because of detection of tubercle bacilli in the urine), which, on gross examination later by the pathologist, reveals no evidence of tuberculosis. Many such cases have been recorded as instances of excretory bacilluria.

The error in this gross pathological diagnosis was detected by Medlar (1924), who pointed out that a microscopic lesion was capable of ulcerating into a renal tubule and discharging bacilli into the urinary stream. Thus, careful examination of serial sections was necessary to find the source of the bacilli in these cases. With Sasano, Medlar confirmed this conclusion experimentally. The two investigators performed intravenous inoculation of a series of guinea pigs with virulent tubercle bacilli. Subsequently, tuberculous bacilluria developed in several animals, and in each case the animal was found to have tuberculous lesions, some of which might not have been detected without examination of serial sections.

Further evidence from clinical data was offered by Harris (1929), who studied the cases of 43 adults and 67 children who were under treatment for surgical tuberculosis, chiefly of bones and joints. He found an incidence of 38 per cent of tuberculous bacilluria in adults and 13.8 per cent in children, most of whom did not have urinary symptoms. Daily, simultaneous urinalysis and cultures of the blood for ten days of three of these patients revealed tubercle bacilli (by inoculation of guinea pigs) in the urine but not in the blood. Harris pointed out that tuberculous bacteraemia, so severe and constant as to infect the urine to this degree, could not exist without the occurrence of miliary tuberculosis, and concluded that the bacilli came from foci of renal tuberculosis.

Recently Feldman, while studying the pathogenicity for the dog of *Mycobacterium avium*, demonstrated the organism in a catheterized specimen of urine taken twenty hours after the animal had received intravenously 8 cc. of a suspension of the microörganisms.

In the work to be reported, guinea pigs and rabbits were given intravenous injections of acid-fast bacteria, and attempts were then made to recover the organisms from the urine of the animals. The guinea pigs were given injections of *Mycobacterium tuberculosis avium* and the rabbits of *Mycobacterium phlei*. *Mycobacterium avium* is relatively nonpatho-

genic for guinea pigs, and *Mycobacterium phlei* is innocuous for rabbits, and both resemble morphologically the tubercle bacillus that commonly causes human infection. In addition, both forms can readily be detected by cultural methods. With these facts in mind, the organisms chosen seemed ideally suited for the purpose of testing the permeability of the kidney for the acid-fast group of bacteria.

EXPERIMENTS

We attempted to plan our experiments in such a way that we could not only detect the passage of any acid-fast organisms through the kidney but could also tell at what time in the course of the experiment this passage had occurred. For this reason, the animals were catheterized at set intervals and the specimens of urine withdrawn were cultured separately on a medium which was known to be suitable for the organism used. In this way more than 500 cultures were made during the course of the experiments. Further, in order to overcome the confusion that might be caused by bacilluria secondary to the development of lesions, the experiments were terminated before this factor could be introduced. To exclude the possible presence of saprophytic acid-fast organisms in the urogenital passages of the animals, control cultures were made before the animals were inoculated, and the samples of urine used were examined microscopically for erythrocytes, leucocytes and non-acid-fast bacteria.

It was found early in the work that occasionally the urethra or bladder of an animal would be traumatized in the process of catheterization, and that blood would appear in the urine. These animals were usually killed by chloroform at that time, athough in some cases the experiments were carried on purposely to introduce this error for the sake of comparison. Each specimen was examined microscopically at the time of culturing.

The first experiment was carried out on guinea pigs with the organism named and by the method described earlier in the paper. It was felt that the duration of the experiment could safely be extended for a week without the possibility of the development of renal lesions. The strain of *Mycobacterium avium* used was an original one isolated by Feldman, and used by him in his work on the dog. It has been typed frequently and still conforms to the general characteristics of the avian strain of the acid-fast group of microörganisms, being markedly pathogenic for chick-

ens and rabbits. Because it grows quickly and profusely on Corper and Uyei's potato medium, this medium was used in all the work.

In the second experiment our intention was to overcome, if possible, any physiological obstacle to transrenal excretion of acid-fast organisms and to make hourly observations and cultures of the urine. With this in view it seemed desirable to use an extremely large dose of the infecting organisms. Rabbits were used, and, since *Mycobacterium avium* is pathogenic for the rabbit, we used the nonpathogenic *Mycobacterium phlei*

TABLE 1

(Experiment 1)

Cultures of catheterized urine from guinea pigs after intravenous injection of a suspension of Mycobacterium avium

GUINEA PIG	CULTURES OF URINE								CULTURES OF HEART'S BLOOD	CULTURES OF TISSUE				
	Control*	Hours after injection†								Liver	Fetus	Placenta	Bile	Kidney
		1	3	5	7	9	24							
1	0	0	0	0	0	0	0		+	+	0	0		
2	0	0	0	0	0‡	0	0‡		+	+				
3	0	0	0	+	0	0	0							
		Days												
		1	3	4	5	6	7	8						
4	0	0	0	0					+				0	
5	0	0	0	0	0	0	0	L	+					
6	0	0	0	0	+	0	0	0	+	+				0

* Culture obtained before introduction of bacterial suspension.

† In this and other tables: 0 = negative; + = positive; a blank space = culture not made; L = culture lost.

‡ Microscopic examination of the uncentrifugated specimen revealed both erythrocytes and leucocytes. In all other cases the microscopic examination was negative.

from a stock strain. In this case the animals were appropriately controlled while hourly specimens were being collected, and the catheter was allowed to remain in position for the duration of the experiment, so that, as far as possible, the factor of trauma consequent to reintroduction of the catheter might be excluded. In this way a continuous flow of urine was obtained; the urine was divided into portions which were cultured and examined microscopically.

Experiment 1: Six healthy adult female guinea pigs were used. Each animal was catheterized and the specimen so obtained was used as a control. Each

animal then received intravenously 0.5 cc. of a suspension prepared from a three-weeks-old culture of *Mycobacterium avium* which had been diluted to a density of 4 on the McFarlane nephelometer scale.

The animals were now divided into two groups (table 1).

The animals in group 1 were all catheterized one, three, five, seven, nine and twenty-four hours after injection, when all were killed. Each specimen of urine was examined microscopically, treated with 5 per cent oxalic acid according to the technique of Corper, and then cultured on Corper and Uyei's crystal-violet-glycerine-water-potato medium.

The animals in group 2 were catheterized at daily intervals, exclusive of the second day. One animal was killed on the fourth day, one on the seventh day and one on the eighth day of the experiment. The urine in every case was treated and cultured as described.

When the animals were killed, the urinary bladder was always found to be empty, and consequently specimens were not obtained. The heart's blood was cultured on Corper and Uyei's medium. The cultures were examined at intervals and were discarded after ninety days.

The control specimens were divided into two equal portions. One portion was cultured directly, without any preliminary treatment for removal of organisms other than the Mycobacterium, while the other portion was treated according to the technique of Corper. In all cases there was a profuse growth of presumably saprophytic non-acid-fast organisms on the medium inoculated with the untreated inoculum, whereas the treated specimens were uniformly negative.

Cultures of the heart's blood taken at necropsy were all positive, and in only two cases were tubercle bacilli detected in the specimens of urine obtained during the course of the experiment. One of these positive cultures was obtained from guinea pig 3, five hours after injection, and the other was obtained from guinea pig 6 on the fifth day of the experiment. In both cases the growth was very sparse and was observed only after some weeks had elapsed. The organisms obtained in this way were typical of the strain used for the original injection, and were found to be pathogenic for tuberculin-tested chickens.

Experiment 2: One adult male and one female rabbit were used. Their bladders were emptied by catheterization and the specimens so obtained were used as controls, half of the specimen being cultured directly and half after treatment by Corper's technique as described in the first experiment. Both of the rabbits then received an intravenous injection of 5 cc. of a heavy emulsion of *Mycobacterium phlei* from a culture four days old. In one of the rabbits the catheter was left in place while the urine was collected continuously. This urine was divided into one-, two- and three-hour specimens, centrifugated, examined microscopically, and cultured. The catheter was then withdrawn.

Twenty-four hours after commencement of the experiment the animals were killed, their abdomens opened, and the urinary bladders seared. The urine was withdrawn and was treated as the hourly specimens had been.

All the samples of urine collected during this experiment were concentrated by centrifugation at high speed for thirty minutes, and the sediment so obtained was treated with 5 per cent oxalic acid and cultured on the medium of Corper and Uyei. The heart's blood was likewise cultured on a similar medium.

In only one instance of the total of eight attempts was a positive culture of acid-fast bacteria obtained from the urine (table 2). This was obtained from the urine of rabbit 1 during the second hour. Cultures made from the heart's blood at necropsy were productive of luxuriant growth in both cases.

TABLE 2

(Experiment 2)

Cultures of catheterized urine from rabbits after intravenous injection of a suspension of Mycobacterium phlei

Rabbit	CULTURE OF URINE*								CULTURES OF HEART'S BLOOD
	Control		Hours after injection				At necropsy		
	a	b	1	2	3	24	a	b	
1	0	C	0	+	0†	0	0	C	+++
2	0	C					0	C	++

* a = treated with 5 per cent oxalic acid; b = untreated; and C = contaminated.

† Microscopic examination positive for erythrocytes.

Summary of results of experiments 1 and 2: An acid-fast organism which resembled in every way that used for intravenous injection was recovered from the urine of 2 of the 6 animals used: from guinea pig 3 at the fifth hour after injection and from guinea pig 6 also at the fifth hour after injection.

A typical culture of timothy-grass bacillus was obtained from the urine of rabbit 1 during the second hour after injection.

In none of these cases was there any microscopic evidence to suggest the possibility of trauma or other abnormality of the urinary tract, and this was felt to be sufficient proof that the organisms had not been introduced by contamination from the blood-stream.

It was considered that this work was not sufficiently conclusive to afford any final deduction; therefore additional experiments were planned with the purpose of exaggerating the factors which would tend to increase the possible renal excretion of the organisms.

It was thought that an increase in the number of organisms in the blood-stream would be the most probable method of increasing the possibility of filtration; accordingly, the quantity of the bacterial suspension was doubled. Otherwise the details of the experiments were as nearly as possible similar to those of experiments 1 and 2.

Experiment 3: Six guinea pigs were inoculated, and experiment 1 was repeated as nearly as possible, except that only three observations were made on the first day, at one, two and five hours after injection, and all the animals were observed at the same intervals until they were killed. The amount of the suspension of organisms also was doubled; thus, each animal received 1 cc. of a suspension of *Mycobacterium avium* comparable to the fourth tube of the

TABLE 3

(Experiment 3)

Cultures of the catheterized urine from guinea pigs after intravenous injection of a suspension of Mycobacterium avium

GUINEA PIG	CULTURES OF URINE*											CULTURE OF HEART'S BLOOD
	Control		Hours after injection			Days after injection					NECROPSY	
	a	b	1	2	5	1	2	4	5	6	7	
7	0	C	++	+	+	+	+	0	0	+†	+†		L
8	0	C	+	++	++	++	+	0					C
9	0	C	+	+	++†	+†	L†	0					L
10	0	C	+	++†	++†								++
11	0	C	+	+	0†	L†						+	C
12	0	C	+	+	+†	L†						+	++

* a = treated with 5 per cent oxalic acid; b = untreated; and C = contaminated.
† Erythrocytes on microscopic examination.

McFarlane nephelometer scale. The inoculum was prepared from a two-weeks-old culture of *Mycobacterium avium* previously referred to. The animals were killed as follows: one after five hours, two after twenty-four hours, and one after seven days (table 3).

Experiment 4: Experiment 2 was repeated, except that rabbits 3 and 4 received 10 cc. of the heavy suspension of *Mycobacterium phlei* instead of the 5 cc. previously used. The urine was collected from both animals continuously by indwelling catheters, and cultured at intervals as in experiment 2. At the end of the first hour one of the catheters became obstructed; therefore rabbit 3 was killed rather than subject it to the effect of reintroduction of the catheter, and all the urine contained in the bladder was cultured after centrifugal concen-

tration. Rabbit 4 was killed at the end of the fourth hour and the urine remaining in the bladder was cultured following centrifugation. The heart's blood was cultured directly from both animals.

In the case of rabbit 3, cultures were made from the urine at three different periods, whereas seven cultures were secured from rabbit 4.

Results of experiments 3 and 4: In experiment 3, thirty-one observations were made on cultures attempted from the catheterized urine, and of these twenty-six (83.69 per cent) were productive of positive cultures of *Mycobacterium avium* similar to the strain used for the intravenous injection.

Of the 26 specimens of urine which eventually yielded cultures of the acid-fast organisms, seven contained erythrocytes or leucocytes. Four other specimens also contained blood elements. One of these failed to yield cultures of acid-fast bacteria, and unfortunately data are not available on the remaining three specimens of urine which gave evidence that trauma had been sustained.

Experiment 4 was unsatisfactory from a technical standpoint, but in spite of this positive cultures were not obtained.

The heart's blood was cultured directly in four cases in experiment 3, and in both cases in experiment 4. Both of the latter cultures were positive, whereas two of the former were positive and two were contaminated.

The results in experiment 3 were so strikingly at variance with the generally accepted ideas concerning excretory bacilluria that it was decided to perform a fifth experiment similar in most respects to the first and third experiments, except that we would attempt to rule out the factor of slight trauma as far as possible by dispensing with catheterization.[3] Therefore, it was decided to use a larger group of animals and to kill them at intervals after injection comparable to those after which catheterization had been done in experiments 1 and 3.

Experiment 5: Eighteen adult male guinea pigs were used, and these were divided into two groups: one of 12 and one of 6 animals (table 4). The 12 animals received intravenously the same amount of *Mycobacterium avium* in suspension as did the animals in experiment 3. The six animals received an equivalent amount of a suspension of *Mycobacterium phlei.*

[3] In contemporary work to be reported, as well as in our postmortem observations in the present study, we had found that it was usually possible to obtain a sufficiently large urinary specimen at necropsy for both cultural and microscopic observations.

Groups of three animals, consisting of two from the first and one from the second groups, were killed at intervals of one, three, five, twenty-four, forty-eight and one hundred and ninety-two hours. Each animal's abdomen was opened by an incision in the median line, the urinary bladder was seared with a hot spatula and the urine was withdrawn by means of a syringe and needle. The urine was now treated with oxalic acid and cultured, and microscopic examination of the sediment from each sample was carried out to detect possi-

TABLE 4

(Experiment 5)

Cultures of urine at necropsy from guinea pigs after intravenous injection of a suspension of Mycobacterium phlei and Mycobacterium avium

GUINEA PIG	CULTURE OF URINE	CULTURE OF BLOOD AT NECROPSY	TIME BETWEEN INJECTION AND NECROPSY
Group 1: Mycobacterium phlei			
13	0	++	1 hour
14	0	++	3 hours
15	0	++	5 hours
16	0	++	24 hours
17	0	C	48 hours
18	0	0	8 days
Group 2: Mycobacterium avium			
19	0	+++	1 hour
20	0	++	1 hour
21	0	++	3 hours
22	0	0	3 hours
23	0	++	5 hours
24	0	+	5 hours
25	0	0	24 hours
26	0	0	24 hours
27	0	0	48 hours
28	0	+	48 hours
29	0	0	8 days
30	0	0	8 days

ble abnormalities. The heart's blood was cultured directly on the potato medium of Corper and Uyei as soon as the bladder had been emptied. The kidneys were preserved for future study, and portions of the liver, spleen, and lungs were preserved for histological examination.

Eighteen specimens of urine obtained at necropsy were examined microscopically and culturally, and in no case was any abnormality found or any culture of acid-fast bacteria obtained.

Eighteen cultures were made from the heart's blood at necropsy; ten of these were positive, one was contaminated, and seven were negative.

SUMMARY

A series of experiments was performed for the purpose of demonstrating if it were possible to bring about passage of acid-fast bacteria through the normal kidney.

Two experiments were carried out first: in one, guinea pigs were given intravenous injections of a heavy suspension of *Mycobacterium avium*, and in the other, rabbits were similarly given injections of a heavy suspension of *Mycobacterium phlei*. The urine of these animals was collected by catheterization, examined microscopically, and cultured by appropriate means for the demonstration of acid-fast bacteria. From two guinea pigs and one rabbit cultures of organisms similar to those injected were obtained from the urine.

Two further experiments were performed, similar to the first two, except that the number of bacteria was doubled in an attempt to obtain more striking results. The results were negative in the case of the rabbits, but 82 per cent of the cultures made from the urine of the guinea pigs were productive of bacterial growth.

Finally, a fifth experiment was carried out, similar to the two experiments on guinea pigs except that the urine was collected by aspiration of the bladder at necropsy. A further change was made by introducing a group of guinea pigs in which *Mycobacterium phlei* was used in place of *Mycobacterium avium*. Positive cultures were not obtained in this experiment. Consequently it was considered that the positive results of the first experiments were due to contamination of the urine by blood elements which had been liberated through abrasions caused by the introduction of the catheter.

We would conclude, therefore, that the normal kidney of the rabbit and the guinea pig is not permeable to the acid-fast organisms used in this investigation, even in the presence of marked and continued bacillaemia.

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THE FREQUENCY OF TUBERCLE BACILLAEMIA BY LOEWENSTEIN'S METHOD[1]

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The question of bacillaemia in tuberculosis has always been a subject of discussion since 1866 when Villemin withdrew blood from the femoral artery of a tuberculous rabbit and also used blood drawn by leeches from a phthisical patient and injected each into guinea pigs and thus transmitted the disease. Weichselbaum in 1884 found the bacilli in miliary cases. Then, in 1891, Liebman demonstrated the presence of tubercle bacilli in blood-smears of tuberculin-treated patients, and, from then until 1915, a high percentage of results was obtained with this method by various workers. However, conflicting results were had from a parallel series of guinea-pig inoculations and were further questioned by demonstrations of bacilli in the blood of normal individuals. A further study revealed the fact that these apparently remarkable results were due to errors in technique; for acid-fast rods were demonstrated in water, fragments of red blood cells were shown to take on the stain of tubercle bacilli and show acid-fast properties, while the chemical reaction of acetic acid and antiformin was shown to cause appearances simulating acid-fast bacilli.

The method of demonstrating tubercle bacilli in the blood from simple smears fell into disuse and gave way to animal inoculations as a means of demonstrating the organisms. By this method tubercle bacilli were found in about 6 to 7 per cent of acute and chronic cases, while miliary cases yielded 66.6 per cent positive results. Nevertheless, the results in the hands of many workers varied widely, some believing that a tubercle bacillaemia was of frequent occurrence while others maintained that it was relatively infrequent. The probable explanation of why tubercle bacilli in the circulating blood are rarely pathogenic for susceptible animals may be due to the scarcity of bacilli inoculated; or probably to the fact that antibodies must be present in the human blood to make the bacilli relatively avirulent or the patient would have developed an acute miliary tuberculosis.

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Because of the slowness and uncertainty of diagnosis by guinea-pig inoculation, the use of cultural methods suggested itself for the demonstration of tubercle bacilli in the blood. In 1917, Mildred Clough grew tubercle bacilli in culture for the first time from the circulating blood of 5 patients with miliary tuberculosis. Ashimura, in 1925, obtained positive blood-cultures from tuberculous patients after their death, while in 1928 Bingold (1) succeeded in demonstrating positive cultures from 3 patients in a series of 48 cases which were studied. In 1930, Russew reported positive cultures in 22 of 25 cases by the use of a new method developed by Loewenstein. Loewenstein (2) isolated tubercle bacilli from patients with tuberculous lesions in the lungs, larynx, kidneys, skin, lymph nodes and bones, even when these patients were clinically afebrile. A tubercle bacillaemia was obtained in each of 5 patients with a subfebrile temperature who were negative on physical examination and X-ray. The diagnosis of tuberculosis was later confirmed by the course of the disease. In active and progressive tuberculosis Loewenstein's results averaged 80 per cent positive cultures. These high results were also obtained in metastatic forms of tuberculosis as long as the process was acute. Animal inoculations in all these cases yielded negative results. Loewenstein concluded that, inasmuch as a bacillaemia can be discovered early in the disease and can be accomplished in a short time, the diagnostic value of the culture method was far superior to that of tuberculin and sputum examinations, and he recommended its general application. The preparation of Loewenstein's culture-medium is as follows:

	gm.
Monopotassium phosphate	1.0
Magnesium citrate	1.0
Magnesium sulphate	1.0
Asparagin	3.0
Glycerin	60.0
Distilled water	1000.0

To each 120 cc. of this solution add 6 gm. potato flour and set in a water-bath for two hours. After cooling to 50°, add four whole eggs and 10 cc. two per cent sterile solution of congo-red or malachite-green, and filter through gauze. Tube and sterilize.

The technique of the culture method is as follows: Collect 10 cc. of blood in 3 cc. of a ten per cent sodium-citrate solution. Centrifugate aseptically. Pour off the plasma. Dissolve the blood corpuscles with sterile acetic acid and centrifugate again. This removes the haemoglobin which, according to Loewenstein, inhibits growth. After repeated centrifugation, the sediment is

washed three times with distilled water to remove the haemoglobin and is then inoculated on the media. If the sterility of the blood is in doubt, treat the sediment with 15 per cent sulphuric-acid solution for five minutes, then add sterile distilled water and centrifugate. After one washing to remove the sulphuric acid inoculate the entire sediment into the tubes.

In a series of 74 cases, attempts were made to demonstrate tubercle bacilli in the circulating blood of tuberculous patients by cultural methods. In 10 cases chosen at random from patients with pulmonary tuberculosis in the Tuberculosis division of Cook County Hospital, Chicago, Illinois, results were negative with the use of Loewenstein's media and method. The medium was then tested with positive sputum to see if it was adequate for cultural use, and colonies of tubercle bacilli were obtained in about three weeks. Then batches of the Sweany-Evanoff and Herrold media were likewise tested for cultural use and were used in addition to Loewenstein's medium, in another series of 55 cases of active far-advanced pulmonary tuberculosis, two of these cases being complicated by tuberculous meningitis. Blood-cultures were taken at various periods of the day, but, in spite of a careful use of Loewenstein's technique with aseptic precautions, results were completely negative. All the sediment was seeded in approximately five tubes of each of the three media in this series of cases. A few difficulties were encountered during the experimental work, in which it was found that all haemoglobin could not be removed from the residue. It was also noted that the sediment, when deposited on the medium, was acid to litmus paper in spite of four preliminary washings with sterile distilled water, although only two are required by Loewenstein's method. In an analysis of Loewenstein's method reported in the *Journal of the American Medical Association* (*3*), it was found that acetic acid, as used, is destructive to small numbers of tubercle bacilli but does not efficiently destroy saprophytic acid-fast bacilli. Therefore, in an attempt to eliminate the acid factor as a detriment to growth, a 1:500 solution of saponin was substituted for acetic acid as a haemolyzing agent, as advocated by Busson (4); but these results were likewise negative in a group of 5 cases. A careful consideration of Loewenstein's method reveals the fact that washings of the sediment are frequent, while the number of bacilli present in the blood-sample itself must be small. Thus it may be possible that the bacilli, relatively few in number to begin with, may be entirely removed by frequent washings. Therefore, as a final attempt, culture-tubes

were inoculated directly with blood taken from 4 cases of active pulmonary tuberculosis. The three types of media were used and all blood from samples of 10 cc. each was inoculated as a very thin film (1 to 2 drops in each tube). However, no growth resulted, although culture-tubes were incubated five weeks, and acid-fast stains were made even with no visible growth apparent. The method was checked by means of controls on normal blood mixed with bacilli and injected into guinea pigs. Cultures on all three media were positive after treating the blood of the inoculated guinea pigs by Loewenstein's method.

A survey of the literature reveals that the results of most authors are in general accord with ours. Of 35 reports reviewed, twenty-two were totally negative or showed a very low percentage of positive results. Of the 13 case-reports showing positive results, six questioned their own results and were uncertain as to their significance, for tubercle bacilli were demonstrated not only in tuberculosis, but also in many other conditions, such as lupus erythematosus, erythema nodosum and induratum, choroiditis, sympathetic ophthalmia, acute and chronic polyarthritis, chorea, multiple sclerosis, retrobulbar neuritis and dementia praecox. The reliability of Loewenstein's method was also questioned in two reports of blood-samples. Both workers (5) (6) sent blood samples to each of two laboratories in Vienna, namely Loewenstein and Monesch, where the results as obtained varied in each laboratory, Loewenstein reporting two or three times as many positive results as Monesch, each laboratory using one-half of the same blood-sample. Why should the results differ in each of two reputable laboratories? Other questions must also be answered: Are all acid-fast bacilli isolated from the blood true tubercle bacilli? Does the demonstration of bacilli prove in every case a true bacillaemia? Is the virulence in the blood the same as in the foci? Are antibodies demonstrable in bacilliferous blood?

Caussimon states that it is probable and possible that, in the course of pulmonary tuberculosis, discrete bacillaemias are produced which escape imperfect technique and which bring on unimportant pathological changes, while Loewenstein believes that the tubercle bacillus causes not only tubercles but also nonspecific inflammations. A bacillaemia is apparently not a permanent condition, since the blood is frequently free even in febrile and progressive tuberculosis. How is the frequency of tubercle bacillaemia in rheumatism to be explained? Reitter and Loewenstein (7) believe that acute rheumatism is an acute inflammatory phase in the course of a tuberculous reinfection. However, the more

likely explanation would attribute the occurrence of a tuberculous bacillaemia in rheumatism and other acute infections to a disturbance in the equilibrium between the attack by the tubercle bacillus and the defensive power of the organism. How are differences in results by various authors to be explained? Mishulow and Park (8) in work on guinea pigs noted that a rapid localization of bacilli occurred when inoculated into the blood-stream, with a steady decrease up to the fourth day. Organisms persisted throughout the course, but fluctuated daily with a marked rise on the day of death. They concluded that there is probably a steady dissemination from the local lesion into the blood-stream. Karwacki (9) noted that repeated passage of a strain of bacilli through guinea pigs and recovery from their blood resulted in a type of bacillus which produces septicaemia without tubercles. After such repeated passage, the bacilli decrease in virulence, lose their acid resistance and change their form. These may be factors to explain the difference in the results. Deist (10) offers the explanation that the rarity of a positive blood-culture was not the result of an unsuitable culture medium, but attributes it to the fact that blood cannot be examined often enough. In experimental work the urine was studied as an index of bacillaemia. In 31 cases, negative by Loewenstein's method and examined for twenty-five successive days, Deist found 12 positive for bacilli, although these were inconstant. No tuberculosis of the urinary or genital organs was noted in these cases. Gualdi attributes the infrequency of detecting bacillaemia as due to inefficient laboratory methods. Kirchner and Li (11) question the value of removing the haemoglobin from the blood which, according to Loewenstein, interferes with the growth of tubercle bacilli. These authors offer experimental evidence to show that neither serum, plasma, nor whole blood have any bactericidal action on tubercle bacilli. They state that since, in the usual culture-methods, only a very limited amount of blood can be seeded, a minimum of 100 bacilli per cubic centimetre must be present in order to yield cultures. Busson (12), in a discussion of media, believes that more than 25 per cent of egg media are contaminated by various acid-fast organisms.

SUMMARY

1. The development of methods for demonstrating bacillaemia in tuberculosis is given.

2. In a series of 74 cases of pulmonary tuberculosis attempts to demonstrate tubercle bacilli in the blood-stream by cultural methods were completely negative.

3. The results of most workers make it apparent that the use of Loewenstein's method is seriously open to question as to efficiency for use in the demonstration of a tuberculous bacillaemia.

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A STUDY OF INCIDENCE OF PULMONARY TUBERCULOSIS

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Incidence is one of the epidemiological factors in pulmonary tuberculosis upon which there has never been agreement, and which has naturally created a good deal of interest and speculation. Physical examinations or tuberculin tests have obvious shortcomings as criteria of tuberculous pulmonary infection, particularly among adults. Groups of school-children have been X-rayed routinely in some localities and in a few other groups this same procedure is being followed, but to date there has not been reported any routine serial roentgenological study made upon a large number of individuals in adolescent and adult life. Such a report is recorded here.

Since, October, 1927, each applicant for *employment* at the Home Office of the Metropolitan Life Insurance Company in New York City, and, at the annual examination since March,1928, each Home Office *employee* have received, in addition to an average careful and thorough physical examination, a fluoroscopic examination of the thoracic organs. Whenever suggestive signs were elicited by physical examination, or questionable or definite abnormalities were seen under the fluoroscope, stereoscopic chest films were taken. Actually about 10 per cent of the entire group so examined have been X-rayed. Interpretation of the films has followed recognized and accepted standards, but we should like to emphasize that it has always been our firm conviction that anything less than a definite and characteristic pulmonary lesion should not be classified as tuberculous. For this reason, it is conceivable that some roentgenologists might classify a few of our so-called "observation" cases, which are not reported here, as minimal tuberculosis; almost certainly none would classify as less than positive those which we have called tuberculous.

From October, 1927, to January, 1933, 17,947 applicants for employment were examined at the Home Office, a group made up of 95 per cent

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girls and 5 per cent boys, the majority about 18 years old. Table 1 shows the findings in this group.

TABLE 1

YEAR	NUMBER OF APPLICANTS	TUBERCULOSIS BY X-RAY	PER CENT
October–December, 1927	1,348	15	1.11
1928	4,405	53	1.20
1929	4,780	35	0.73
1930	3,105	28	0.90
1931	2,175	25	1.15
1932	2,134	28	1.31
Total	17,947	184	1.03

Whenever a definite lesion characteristic of pulmonary tuberculosis was evident on the X-ray film, an effort was made to reëxamine and question the applicant carefully, to determine, if possible, the source of infection, as well as the clinical condition, before referring him to his own physician or to a tuberculosis clinic. Of the 184 applicants who had a positive X-ray, 51 were classed as active after reëxamination, 79 were questionable, and 54 did not return for reëxamination. If, however, these same proportions held in those not reëxamined, there were 72 active cases in need of immediate treatment and the remainder were in need of careful observation.

On January 1, 1933, there were at the Home Office 14,054 employees, of whom about 5,000 have had one or more X-rays of the chest since 1926. In this group there were 501 individuals whose X-ray films disclosed definite evidence of a lesion characteristic of pulmonary tuberculosis. The *clinical* condition of these employees is not considered here.

Of these 501 individuals, 70 per cent have undergone a "cure"; the great majority at the Company Sanatorium at Mount McGregor, New York, a few at some other tuberculosis sanatoria or at home under the care of their family physician. The remaining 30 per cent, who by X-ray examination showed a characteristic lesion, had at no time realized that there had been any disease of the lungs. They denied all symptoms, had never undergone a cure, and simply showed by X-ray examination evidence of pulmonary tuberculosis. The majority of this latter group showed no clinical signs of activity and have remained at work under observation. A detailed description of these cases is given in tables 2 and 3.

TABLE 2

Pulmonary tuberculosis among Home Office employees, January 1, 1933

	TOTAL	CURED OR CURING AT M.L.I. CO. SAN.	CURED OR CURING ELSEWHERE	NEVER TOOK CURE
Total	501	334	15	152
Minimal	272	158	7	107
Moderately Advanced	188	138	7	43
Far Advanced	41	38	1	2

Total Home Office employees: 14,054.
Per cent tuberculous: 3.6.
(Question of clinical condition not considered here.)

TABLE 3

Tuberculosis of respiratory system (active, activity questionable, healed) Home Office employees, Metropolitan Life Insurance Company, January 1, 1933; incidence rates per 100; ages 17 to 69 years

ALL AGES	MALES			FEMALES		
	Number of Employees	Tuberculosis Incidence	Rate per 100	Number of Employees	Tuberculosis Incidence	Rate per 100
	4,005	213	5.32 (Standardized Rate*) 3.51	10,049	288	2.87 (Standardized Rate*) 3.36
17–19	268	1	0.37	2,422	4	0.17
20–24	901	15	1.66	4,060	80	1.97
25–29	581	22	3.79	1,246	76	6.10
30–34	429	18	4.20	724	42	5.80
35–39	445	25	5.62	502	14	2.79
40–44	417	28	6.71	412	20	4.85
45–49	376	26	6.91	281	18	6.41
50–54	240	24	10.00	211	19	9.00
55–59	172	28	16.28	141	9	6.38
60–64	132	21	15.91	50	6	12.00
65–69	44	5	11.36			

* The difference in distribution of males and females in the various age-groups should be noted (table 3). Because of the dissimilarity of distribution by age of the two groups, the crude incidence rate (i.e., the incidence rate of the whole group) is misleading. Therefore the standardized rate was computed by assuming that the age-distribution was the same for both sexes. This rate shows that the comparative incidence of pulmonary tuberculosis is only slightly higher (3.51 per cent) for the men than for the women (3.36 per cent).

It is interesting to compare the incidence of tuberculosis in this latter group by sex and age with the death-rate from respiratory tuberculosis

of our industrial policyholders, the general character of the two curves being so similar, especially for the males (see chart).

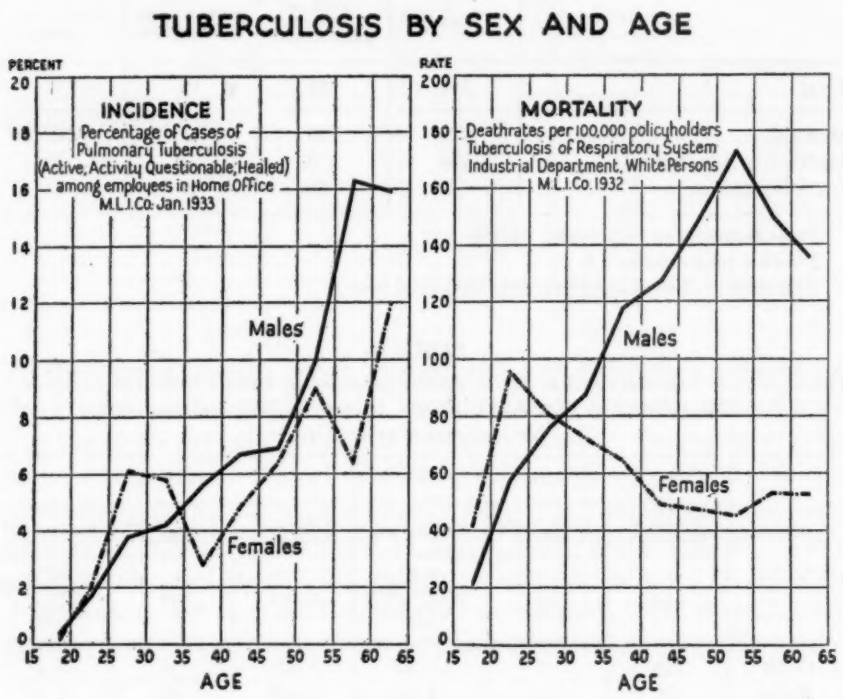


TABLE 4

Incidence of new cases of tuberculosis (active, activity questionable, healed) discovered annually among Home Office employees, years 1927 to 1932, inclusive

YEAR	NUMBER OF EMPLOYEES	NEW CASES OF TUBERCULOSIS	PER CENT
1927	11,192	109	0.97
1928	11,530	106	0.92
1929	11,966	85	0.71
1930	12,468	71	0.57
1931	13,081	72	0.55
1932	13,582	59	0.43

In view of the relatively high incidence of pulmonary tuberculosis discovered by fluoroscopic and X-ray examination in the group of Home Office employees, it may be well to include table 4, which shows that the new cases of tuberculosis have decreased markedly each year since the

introduction of our present routine. The declining number of new cases controverts any fear of hazardous working conditions or contagion from unrecognized sources, and might well be used as an argument in favor of our method of supervision.

The roentgenological survey of these individuals raises several questions. Why is there such a great incidence of tuberculosis by X-ray in this older age-group? Is this group a residue from a heavily infected general population which had such a high death-rate 25 years ago? Is there frequently a reactivation of a primary lesion or a superimposed infection in later adult life? May there be a retention in service of an unusual number of the tuberculous employees? This last possibility may be ruled out, for the labor turnover of those with tuberculosis is about the same as those without tuberculosis.

SUMMARY

There are presented the results of a five-year fluoroscopic and X-ray film study of the incidence of pulmonary tuberculosis in a group of the population, either candidates for or engaged chiefly in office work under favorable health conditions and careful medical supervision.

Among 17,947 young persons, whose average age was about 18 years, there were found 184 (1.03 per cent) cases whose X-ray film disclosed a definite and characteristic tuberculous lesion. Among 14,054 Home Office employees of an older average age (see table 2), there were 501 (3.6 per cent) cases of pulmonary tuberculosis. This observation emphasizes some facts which we have recognized for a long time.

1. Routine careful roentgenological examinations disclose a fairly constant and definite percentage of cases of definite pulmonary tuberculosis among our applicants for employment.

2. A large proportion of these cases in younger persons is apt to be active and in need of immediate treatment and/or careful observation.

3. A surprisingly large number of adults show definite roentgenological evidence of a pulmonary tuberculous lesion. In our experience, relatively few of these individuals have needed immediate treatment, but all need careful observation.

4. Active tuberculosis occurs in older adults more frequently than is generally recognized.

BOOKS[1]

JESSAMINE S. WHITNEY: *Tuberculosis hospitalization in the United States. With 15 tables, pp. I and 38, New York, N. Y., National Tuberculosis Association, September, 1933. Mimeographed.*

By BENSON BLOOM

In 1926 Drolet presented a report on tuberculosis hospitalization in the United States; and the present work is a similar study to discover what improvements have been made in the five-year period, 1926 to 1931. This study is essentially a compilation of the reports obtained by means of a questionnaire sent to all tuberculosis sanatoria in this country, 571 in number, of which 65 per cent returned answers. These represent 72 per cent of the tuberculosis beds in the United States.

In only 18 states was the standard minimum of one bed for each tuberculosis death per year attained; for the entire country the ratio was 1.02 annual deaths per tuberculosis bed in 1931, as compared with Drolet's figure of 1.35 in 1926. The southern states, in general, showed a marked deficiency in beds: in Alabama, for example, there were only 570 beds as compared with 2,327 deaths. In Colorado, Massachusetts, Michigan, Minnesota, New Mexico and New York the numbers of beds far exceeded the deaths per year. Of the total of 82,974 beds in this country for tuberculosis, only 936 were for the

[1] THE REVIEW plans to carry a section devoted to *Book Reviews* from time to time. It accordingly invites contributions of this nature from any authors who may see fit to submit manuscripts and will be glad to accept those reviews that measure up to standards that would comprehend such features as thorough familiarity with the text of the work under review, as well as knowledge of the subject and field covered by the book; apposite comparisons with related texts; critical ability and treatment; good literary form; and helpful description of contents. Uncritical praise and repetition of publisher's "blurbs" will be as undesirable as savage or personal attacks; neither will be tolerated. The main—almost the sole—purpose of an acceptable review should be to inform and to entertain. No limits or restrictions will be set on length of manuscript or manner of treatment provided the above-mentioned general considerations are adhered to. All reviews must be submitted gratuitously and those accepted will be published without compensation. Manuscript should be prepared in standard form (typewritten, one side of sheet only, double-spaced, etc.), and according to the style set in the reviews printed above.

Any opinions expressed are to be considered as those of the reviewer alone, and the widest latitude consistent with probity, ordinary courtesy and fairness will be allowed in this respect. In no way are they to be regarded as representing opinions of the publisher or editors.

In general, reviews will appear under the reviewer's name, initials or pseudonym. If, however, good and sufficient reasons can be adduced, worthy anonymous or unsigned reviews may be published, provided the author's name is known to the editor.—*Editor.*

exclusive use of negroes; for insane and prisoners there were 9,005, for federal patients 9,592, and for the civilian population 63,441. New York State had almost 10,000 beds for civilians, California nearly 5,000. Federal beds were more numerous in Colorado than any other state, 1,621 of the total of 3,966 in that state being devoted to federal patients. In the five-year period civilian beds increased 20 per cent, those for prisoners and the insane increased one-third, while the federal beds decreased 28 per cent. The answer to the question of how many patients were admitted since the opening of the various institutions brought an estimate of 1,371,200 admissions to the sanatoria up through 1931; of these, nearly 7 per cent were readmissions, including "repeaters." From the returns received from 264 institutions, it is estimated that 246,600 patients, or 19 per cent of those admitted, died in the institutions, a result which is not at all astonishing when one realizes the rôle sanatoria play in the case of the tuberculous. In 1926, 84 per cent of the beds available were in use; in 1931 this figure was 94 per cent, the increase obviously being associated with the depression. Since 1926 there occurred an increase in the proportion of beds used by women, and a corresponding decrease in those used by men. An increase in the proportion used by children did not occur, as one might expect from the increased interest in the care of tuberculous children; however, this is easily explained by the fact that children are frequently provided for in special institutions and not as a rule by the type of sanatoria under consideration. It is estimated that in July, 1931, there were 60,300 civilian patients in tuberculosis sanatoria in this country, a figure slightly less than Drolet's estimate in 1926, which included, however, all federal patients. In table 6 the patient census of civilian sanatoria is given, from which it appears that the proportion of unoccupied beds was considerably lower than for general hospitals, there being 60,300 beds occupied of the total of 64,377.

With regard to the length of stay of the patients, it appears that 37 per cent of the patients admitted remained less than 3 months, and 17 per cent less than a month. These figures are approximately the same as those of Drolet, so that it seems that little has been done to eliminate the wasteful practice of admitting patients who leave almost immediately. In the five-year period the average length of stay had increased from 5 months and 3 weeks to 6 months and 13 days. The types of cases differed from those reported by Drolet essentially in that 8 per cent were reported as being of the childhood type, this entity not being sufficiently distinct in 1926 to warrant its differentiation from "pulmonary" tuberculosis. Nine per cent of all the cases were nontuberculous and 2 per cent were undiagnosed; these figures do not differ appreciably from those of 1926. As a result of sanatorium care 58 per cent of the patients were discharged as improved (17 per cent "apparently arrested" and 4 per cent "improved or quiescent"). Nineteen per cent were discharged "unimproved or progressive," and 23 per cent died in the institutions.

The replacement value of the 64,377 civilian beds for tuberculosis was estimated at $212,535,200 or $3,300 per bed; of this amount over $50,000,000 was estimated for New York State. The average cost of maintenance of a civilian bed was $17.50 per week; and the estimated total cost of maintenance of civilian sanatoria in the United States was $58,000,000 per year.

The cost of the care for the individual patients was apportioned as follows: 72 per cent had free beds, 12 per cent paid the full cost of care, and 16 per cent paid part of their expenses. Pennsylvania with 5,714, New York with 5,500, and California with 3,016 had the largest number of free beds. The paucity of free beds reported in some states (New Mexico, for example, with only three) is, one hopes, explicable on the basis of inadequate reports.

The above results are from civilian sanatoria; separate tables are given for Indian sanatoria and various other government sanatoria including those for veterans. In the latter group there were (estimated) 174,200 admissions, since the opening of the institution, 16,000 deaths, and a patient census of 7,600 on July 1, 1931. The replacement value of the buildings and grounds was estimated at over 56 million dollars and the maintenance cost at over 13 million dollars for that year. In this group the average stay in the sanatoria was decidedly shorter than for civilians, 36 per cent leaving in the first month. The percentage of deaths (13 per cent) was less than for the civilian group: the proportion of unimproved or progressive cases (50 per cent) was, however, greater. For the Indian Sanatoria the (estimated) figures are 15,200 admissions, 900 deaths in the institutions, and a census of 910 on July 1, 1931. The patients remained in these sanatoria longer than the other groups (perhaps because of governmental authority or pressure), and the proportion of improved and arrested cases was strikingly higher than for the other governmental sanatoria, and moderately higher than for the civilian sanatoria. The percentages of deaths for the three groups, Civilian, Indian, and other Governmental, are, respectively, 23, 9 and 13 per cent. Similarly, the figures for apparent arrest are 17, 27 and 14 per cent; for improvement they are 41, 44 and 23 per cent. These figures suggest that the better results obtained are attributable to the longer periods of sanatorium care; certainly an explanation on the basis of racial differences of immune reactions is unlikely.

This work is in no way subject to critical review, being entirely factual in its material. Whatever defects it may have are due to failure of some institutions to answer the questionnaire, completely or in part. On the basis of the returns sent in, estimates on the various subjects have been made for the separate states and for the entire country, so that this work will be found to be an excellent reference paper for those interested in the question of tuberculous hospitalization. It is important to remember, however, that the numerous "estimates" may be considerably in error.

P.-F. ARMAND-DELILLE AND CH. LESTOCQUOY: *La tuberculose pulmonaire et les maladies de l'appareil respiratoire de l'enfant et de l'adolescent. In collaboration with* RENÉ HUGUENIN, *with an introduction by* PROFESSOR CALMETTE. *Amédée Legrand, Paris, 1933. 2 volumes, pp. X + 499.*

By MAX PINNER

Within a few years, two monumental works have appeared that are concerned with tuberculosis in childhood. The one, recently reviewed in these pages, has as its field tuberculosis in childhood (Engel, Pirquet, *Handbuch der Kindertuberkulose*); the other (Armand-Delille, Lestocquoy and Huguenin) confines itself to pulmonary tuberculosis in childhood with the addition of some brief chapters of nontuberculous pulmonary disease. The two works provoke comparison. The German book, written by many authors, is encyclopaedic and lacks uniformity; the French work has the closely knit unity and discipline that is apparently the result of well organized coöperation, if not actually the product of one pen; it is not only more limited in its chosen scope but in its points of view as well. The German opus is heavy with theory, controversial opinions and general problems; the French opus is factual and somewhat more dogmatic. Both are richly documented and most beautifully illustrated. But in regard to this point the French work far outshines its German mate; the illustrations are excellent and cannot be praised too highly. This work makes its appearance in the form of an atlas: most roentgenograms and gross pathological specimens are reproduced in natural, or nearly natural size. The majority of them are accompanied by schematic drawings which are very helpful guides for understanding. The reproduction of histological sections would probably be more convincing if they had been made from microphotograms instead of from drawings. The roentgenology and pathology of pulmonary disease in childhood, of tuberculosis in particular, is taught pictorially as completely as it seems to be possible by the method chosen. Since the method of presentation is essentially that of empirical casuistics, it would have been preferable to include in the legends more clinical data pertaining to the specific cases. Instead, the clinical course is discussed in the form of general comments of the various clinical entities.

The text, besides the clear and concise legends, is devoted to general discussions on pathogenesis, clinical features and explanatory theories. The latter embody the current French conceptions, particularly those of Calmette, who wrote the introduction. The reality of the filterable virus is asserted, but the need to refer to it in the further text was obviously absent. The same may be said about transplacental infection, although true congenital tuberculosis might, for completness's sake, have been mentioned. In accordance with Calmette's opinion, inhalation infection is thought to be very rare, and it is stated that tubercle bacilli, regardless of their portal of entry, are likely to focalize eventu-

ally in the lung to produce the so-called primary complex. The latter is considered to be a focus of endogenous reinfection in allergic soil. Why this endogenous metastasis is single in the vast majority of cases, and why it is structurally different from any later metastasis is neither discussed nor explained. The basic dicta on filterable virus, portal of entrance and pathogenesis are treated much in the manner of *Roma locuta, causa finita.*

It would be interesting to speculate on the curious fact that, in spite of fundamentally different basic conceptions, such practical features as diagnosis, roentgenology and treatment are quite similar in the text-books of the various nations. Is this a silent admission of the sovereignity of empiricism, or is it an indication of the failure to take theoretical principles seriously in interpreting observed data?

A chapter of great interest is that on *spléno-pneumonie* (i.e. *epituberculosis, Infiltrierung*); in addition to excellent radiological material, it contains the pathological documentation of two thoroughly studied autoptic cases dead of nontuberculous disease. Pathological data on this clinical entity are rare by virtue of its benignity implied in its definition. The more that becomes known of this condition pathologically, the more it seems doubtful whether epituberculosis is justifiedly represented as a clinical and pathological entity. There seems to be no criterium by which it can be separated from exudative tuberculosis which, possibly on account of high allergy, spreads in its histological manifestations far beyond the site of bacterial focalization and which tends to resorb. The desire to consider *spléno-pneumonie* as a separate entity seems to be caused only by its benignity which, at the time when Grancher first described it and when later Eliasberg suggested the name *epituberculosis*, fitted badly into the then current concept of the invariable gravity of pulmonary tuberculosis in childhood. This concept has since been changed radically so that there is now little call for a terminology that has apparently only an historical significance. Nevertheless, the discussion of *spléno-pneumonie* deserves careful reading just because the benignity of certain forms of pulmonary tuberculosis in childhood has not yet been realized to a sufficient degree.

References to the literature are so casual that their omission would have been preferable; particularly since, in many instances, more authoritative work than some of that quoted could have been cited.

The few critical and sceptical remarks in the preceding paragraphs should not create the impression that the reviewer does not admire the beauty and the completeness of this work as well as the clarity of its clinical, roentgenological and pathological discussions. It is, without doubt, a most important contribution to pediatrics; it is a better substitute for demonstrations and lectures on its subject than any other book that I know. It is one of the chosen few that one wishes to see translated in a sufficient number of different languages,

that it could become common property of all those interested in pediatrics or in tuberculosis.

H. ULRICI: *Diagnostik und Therapie der Lungen- und Kehlkopf-Tuberkulose. Pp. V + 389, with 269 figures. Second edition, Berlin, Julius Springer, 1933, paper. Rm. 25.*

By MAX PINNER

Here is a text-book which should satisfy all requirements that can be reasonably made from a book of definitely limited size. By virtue of its conciseness it is quite complete though brief. The clarity of its expression renders it understandable both for students and practitioners, and the vast clinical experience and the superior judgment of its author succeed in adding wisdom to the discussion of mooted questions. The subjects of pathology and pathogenesis are well presented in the light of modern continental teaching and they are not, as is so often the case, overburdened by theory and hypothesis. One might wish that in some important therapeutical questions the author had done more than relate his experiences; namely, to add more definitely an opinion and recommendation. This is particularly felt in his discussion on tuberculin therapy; it is only by inference that one can deduce that he does not think highly of its therapeutical efficiency. Dr. Ulrici is a strong advocate of collapse therapy in early lesions. The statistics from his institution which have been elaborated by Roloff and which are incorporated in the present book are some of the most valuable ones on this subject. They lend strong support to the author's plea for early interference. In view of this attitude, one is astonished to see numbers of roentgenograms which show marked progressive and destructive changes without any evidence of surgical interference. But, since they are not dated, they may have been collected before the present therapeutical opinions had crystallized.

The book is richly illustrated, both with pathological specimens and roentgenograms. The illustrations are unusually well chosen and no praise can be too high for the excellence of their reproductions. Although the roentgenograms are in part fairly small they are much clearer and much more distinct in all details than those of many roentgenological atlases. It is with a great deal of envy that the reviewer is forced to comment that he does not know of any American publication which approaches the excellence of these roentgenographic reproductions.

Although this book does not pretend to add any particular point to existing knowledge, but only to summarize briefly what a physician should know about pulmonary and laryngeal tuberculosis, it is highly recommended for the study of anyone who can read German with ease.

E. V. McCollum and J. Ernestine Becker: *Food, nutrition and health. Third edition, rewritten, pp. v + 146. Published by the authors, Baltimore Maryland, 1933, cloth. $1.50.*

By AARON EDWIN MARGULIS

To the busy phthisiotherapist the management of nutritional problems is possibly ever a two-fold task. Having answered "What shall I eat?" he may yet be faced with "Why?". To those of his inquisitive patients to whom an intelligent understanding of every outlined procedure is a prerequisite for the fullest coöperation, the physician may with profit and *safety* (indeed a high compliment in these days!) recommend the reading of this exposition of the subject, now appearing in its third edition.

This book fulfils all that may reasonably be expected of a popular treatise. The authors are closely identified with the subject by their researches as well as by being Professor and Associate respectively of Biochemistry in the School of Hygiene and Public Health of Johns Hopkins University. The style is admirably lucid. The discussion carries authoritative conviction and achieves a delineation which the intelligent layman should find truly informative, being not so oversimplified as to leave his questions essentially unanswered nor so dogmatic as to be misleading. The contents include a presentation of the problem, namely, the basic features and desiderata of diet, with perhaps a rather overly-heavy emphasis on vitamins, in sympathy with the current trend; a description of the dietary properties of potential foodstuffs; practical suggestions with tables of food values, menus, and, what is always pertinent though currently accentuated, a consideration of the economic aspects of adequate diet with general rules for permissible comprises between palate, pocket-book and sustenance of health. Excursions into pathological states include discussions of overweight, underweight, hygiene of the digestive tract, dental caries, and acidosis from dietary indiscretion with suggestions for their correction and prevention. The problems of diet in tuberculosis *per se* are not discussed, but this enhances rather than mitigates its usefulness to the phthisiotherapist since it obviates potential disagreements over an as yet controversial subject.

W. Schönfeld and K. Menzel: *Tuberkulose, Charakter und Handschrift. Eine experimentell-statistisch graphologische Untersuchung an Heilstättenpatienten. With 22 illustrations, pp. 98, Brünn, Rudolf M. Rohrer, 1934, paper. Mk. 5.*

By MAX PINNER

The reaction against the complexity of the postwar débacle in Europe has produced some curious mental phenomena that are understandable only on

the basis of the particular experience of that period, which, without its organic connection, are too easily and too uncharitably condemned as insignificant aberrations. One of these phenomena whose importance can hardly be overrated is a profound emotional distrust of the sovereignty and effectiveness of pure reason. Where this distrust, born of bitter disillusion in a crumbling world, invaded those fully equipped for scientific and rational endeavors, it caused a revival of interest in phenomena that for centuries had lingered at the very outskirts of scientific pursuits. No-man's land between science and folk-lore, between rationalism and intuition was entered with passionate interest; and, since the new occupants were, in many instances, men of superior mental equipment, the field was attacked with the instruments of rational science, notwithstanding their distrust of traditional scientific method. What had been motivated by a break with science (that was felt to have failed in the exigencies of life) ended often in a valiant attempt to push forward the outposts of science into territories heretofore beyond the confines of science. Many of such attempts should, and frequently have not been acknowledged, as sincere and potentially legitimate efforts. Their results are so young, so little tested, and certainly so far removed from the *idola fori* of accredited science that they have received hardly any serious attention, particularly in countries, such as the United States, which have not experienced the convulsions of postwar Europe which forced so many departures from acquiescence and tradition.

Characterology and graphology may be properly understood as results of such a break with scientific tradition. The aims and justification of the former are self evident; the latter claims that handwriting is a document of individual characteristics of a high order of reliability. Without holding a brief for graphology, it seems pertinent to recall the fact that a person's signature is accepted as identification, practically without protest. If this is so it is probably no aberrant endeavor to search for the implied intimate connection between personality and handwriting. Only the obtusely unaware person will not receive (and more or less consciously utilize) impressions from a person's facial expression, motions, tone of voice, handwriting, and similar *imponderabilia*. The more recent graphological studies have attempted to replace such impressionistic generalities by minute analysis based on measurable characteristics. That significant results have been obtained with graphological studies on insane patients is common knowledge. The validity of the method in the study of normal psychology is still *sub judice*.

The present monograph appears to be a thoroughly serious effort to apply the graphological method to the complex problem of the psychological influences that tuberculosis exerts as disease and as a vital experience. The reviewer is not competent to judge the accuracy of the particular technique nor the correctness of the results. The purpose of this review is not a discussion of the actual results of this coöperation of a physician and a graphologist,

but to point out the potentiality of graphology becoming a mode of approach to the problem. The reader who is totally uninitiated in modern graphology must accept the validity of the method which is neither explained nor justified in this essay; he may judge in a vague and broad manner whether the results of these studies on 400 patients warrant further study. If he arrives at a positive answer he may find interest in acquainting himself with the methodological principles in such books as that of L. Klage, *Handschrift und Charakter*.

BRONCHIAL STENOSIS IN PULMONARY TUBERCULOSIS[1]

With Some Notes on Tuberculous Stenosis of the Trachea and the Bronchioles

LEO ELOESSER

Stenosis of the larger air-passages has been a step-child of clinical medicine. Interest in it is but recent, it is still recognized too rarely; not many of us, I think, are aware of how frequently it occurs.

MORBID ANATOMY

Tuberculosis may be responsible both directly and indirectly for stenosis of the bronchi. If we list stenoses according to the classification of v. Schroetter (1), the obstruction may lie intramurally, murally and extramurally. Of these, intramural obstruction is the least frequent; the offending tuberculous lesion usually lies in or near the wall rather than in the lumen. However, there are intramural lesions. In children, especially, a peribronchial or peritracheal lymph node may suppurate and ulcerate the bronchial wall; a greater or lesser part of it may slough out into the bronchial lumen, causing a sudden fit of strangling and cough, during which the offending piece of lymph node may be coughed out. Numerous such instances have been recorded in the pediatric literature (2).

Mural processes are more frequent. They may take the form of a caseous ulcer (figure 1) or of a hyperplastic submucous infiltrate (figure 2) producing a thickening of the wall of the air-passages sufficient at times to obstruct their lumina; submucous tuberculous granulomata (figure 3) with hyperplasia of the submucous lymph follicles may cause obstruction; and finally fibrous scars may so kink and distort the bronchial wall that the lumen is closed. These three manifestations of bronchial tuberculosis—the ulcerative, the hyperplastic and the shrinking, may coexist in various places of the same bronchial tree.

Extramural processes are also frequent. Enlarged hilar lymph nodes may compress the bronchial wall, and peribronchial sclerosis may kink

[1] From the Stanford Surgical Service of the San Francisco Hospital, Department of Public Health, San Francisco, California.

and distort it (figure 4). This sclerosing peribronchitis is more often nontuberculous; it is often syphilitic (figure 5); it is not infrequently found when syphilis or other chronic sclerosing infections accompany tuberculosis.

Besides these three main divisions, there is a fourth form in which the

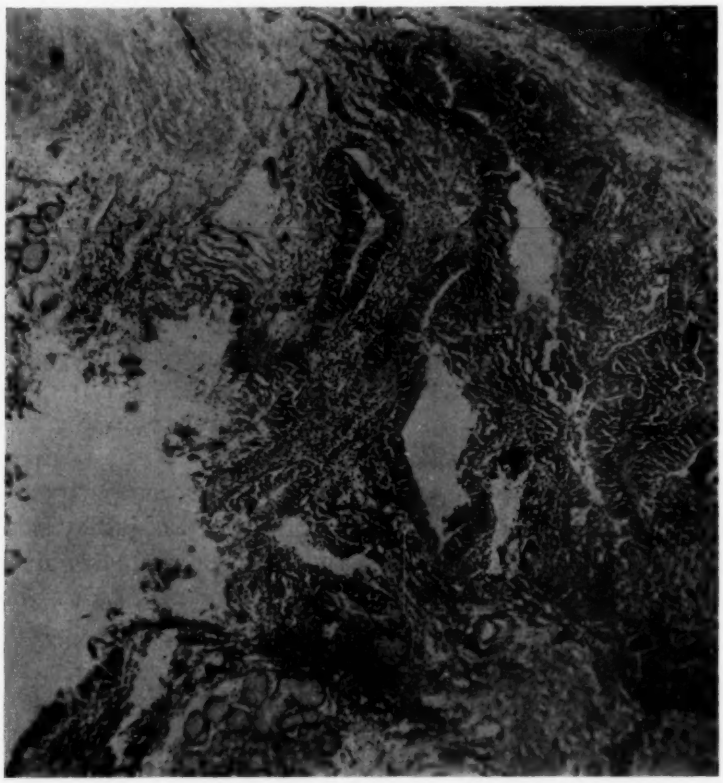


FIG. 1. Acute ulcerative tuberculous bronchitis. Ulceration of mucosa. Tubercles with giant cells.

smaller bronchi are more or less diffusely obliterated, comparable to the *Bronchiolitis fibrinosa* which Fraenkel (3) found in persons exposed to the fumes of corrosive gases (figure 6).

Caseous ulcers of the greater air-passages undermine the mucosa and may destroy the wall; accompanying oedema and inflammatory swelling may obstruct the lumen; hyperplastic tuberculous infiltrates are less well known. The mucous membrane over them is thickened, but fairly

FIG. 2. Tuberculous tracheitis, with granuloma containing epithelioid tubercles and areas of caseation.

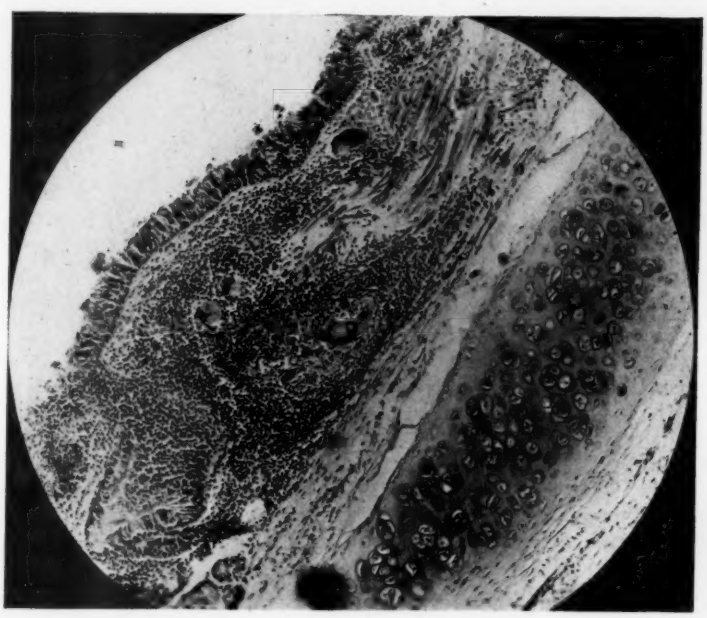


FIG. 3. Tuberculous bronchitis. Submucous tubercles with giant cells

smooth; under the mucosa there is a dense, white, scarry layer of cartilaginous hardness. This form bears the same relation to the ulcerative

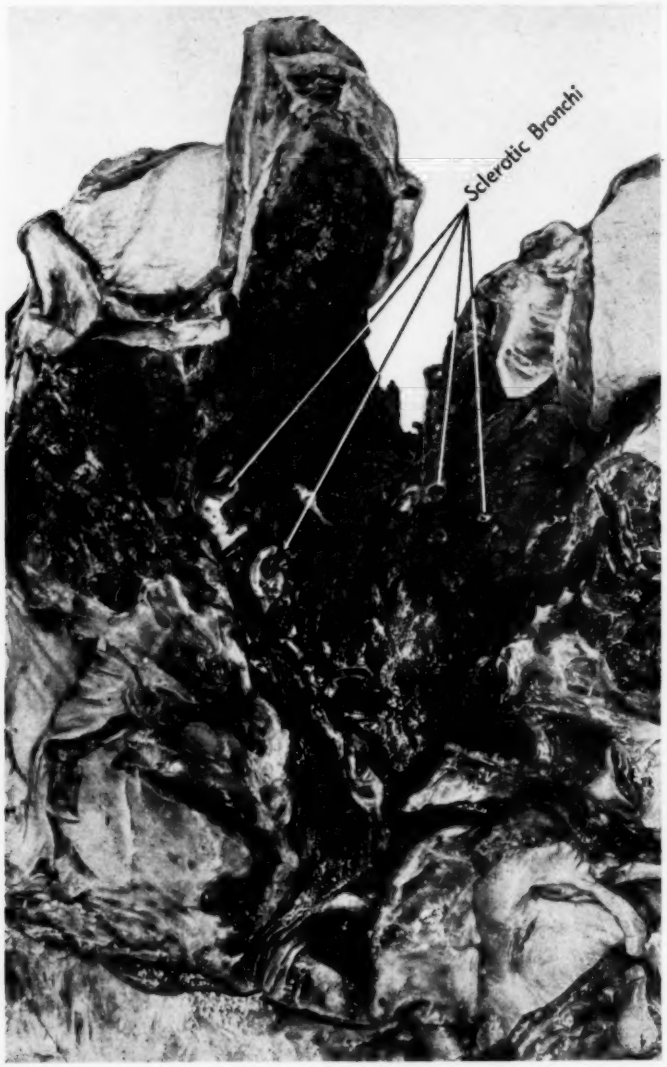


FIG. 4. Peribronchial sclerosis. Dense white scars surround the cut-sections of bronchi which pierce an atelectatic parenchyma.

one as the tubercular ileocaecal tumor does to an ulcerative tuberculous ileotyphlitis.

Peribronchial sclerosis differs again from this hyperplastic form in that the scar lies not in the bronchial submucosa, but outside the bronchial wall; it may be that it represents the end-result of an invasion of the peribronchial lymph-channels. It is less constricting than deforming, and obstructs the air passages by kinking and distorting them. One finds it less in tuberculous than in nontuberculous affections. It has been

FIG. 5. Peribronchial sclerosis. Dense masses of fibrous tissue surrounding the bronchial cartilages.

minutely described by Schmorl (4) and his pupil, Gey (5), under the name of *Bronchitis deformans*. It may be that the syphilitic peribronchitis of Benda (6) and other French authors represents the same pathological development.

Surgical procedures designed to collapse the lung are not infrequently at fault; if the lung is fibrous or consolidated before operation, thoraco-

plasty or paraffin filling may transmit pressure on to the larger bronchi and close them off, or the deformity resulting from operation may twist or kink the bronchi by the pull of fibrous bands running from the chest-wall toward the hilum. It seems not impossible that the atelectasis and fibrosis which follow any form of efficient collapse therapy, even pneumothorax or phrenic interruption,[2] may lead secondarily to persistent deformity, which in its turn may cause stenosis of the larger air-passages.

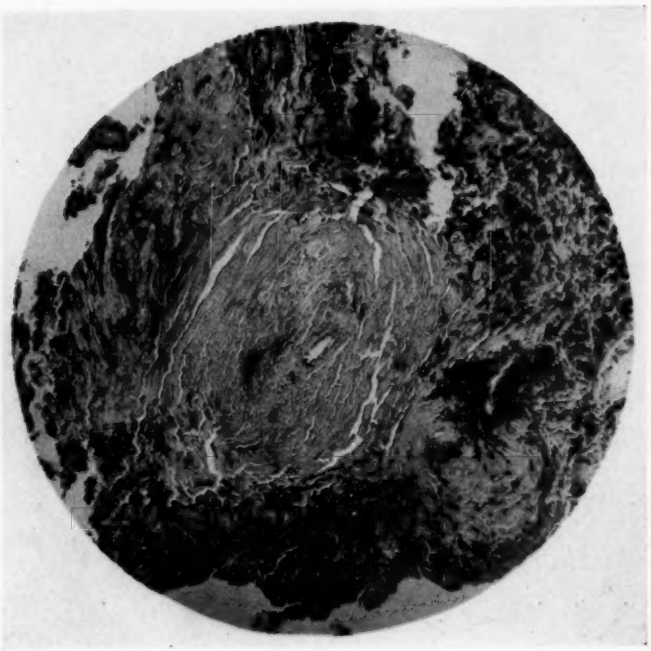


FIG. 6. Stenotic bronchiolus from case of diffuse obliterating bronchiolitis, showing peribronchiolar sclerosis with surrounding inflammatory deposits and atelectasis. (Case 17.)

More often than not, both at the bedside and at the autopsy table, the stenoses are complicated by suppurations and infections which lie distal to the stenosis. Septic secretions, able to drain imperfectly or not at all, give rise to abscess cavities, bronchiectases with purulent content, and to inflammatory swellings and congestion, which mask and complicate the picture of simple stenosis.

The tuberculous hypertrophies and ulcerations just described are of

[2] Personal communication of Dr. Schaper.

necessity more or less localized to smaller portions of the bronchial tree. A diffuse stenosing process, affecting not small portions of the larger air-passages, but large areas of the bronchioli, is often found in tuberculosis superimposed on chalicosis in stone cutter's lung. Here the lumen of many, if not most of the bronchioli, is closed by chalicotic or tuberculous granulations and scar.

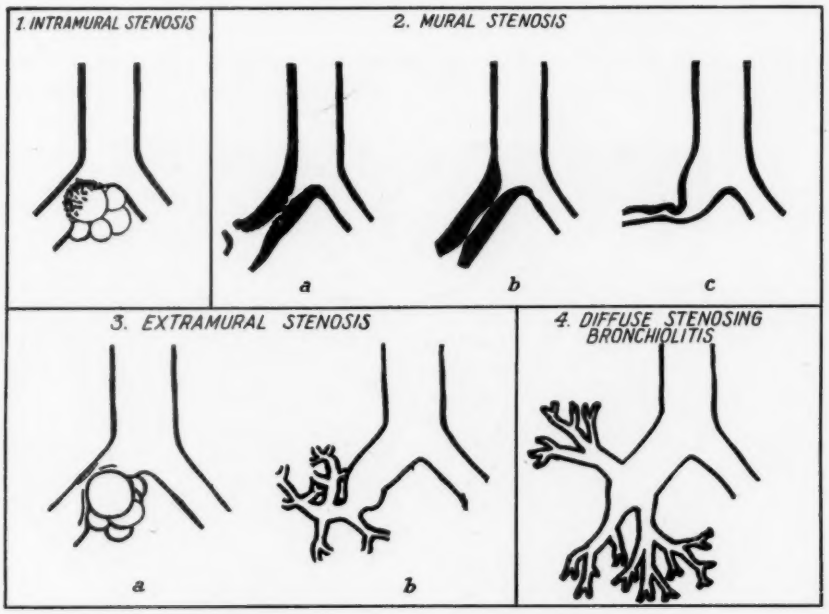


FIG. 7. Types of bronchial stenosis:

1. Intramural stenosis; ulcerating lymph node extruded into bronchial lumen.
2. Mural stenosis.
   a. Caseous ulcerative bronchitis.
   b. Submucous hyperplasia.
   c. Sclerotic shrinkage and distortion of bronchial wall.
3. Extramural stenosis.
   a. Extramural compression by enlarged peribronchial lymph nodes.
   b. Peribronchial sclerosis with extramural distortion and compression.
4. Diffuse stenosis of smaller air-passages (obliterative bronchiolitis).

PATHOLOGY OF FUNCTION

Chronic obstruction of the air-passages, whatever its cause, produces certain changes in the obstructed lung and also certain disturbances of respiration.

Total obstruction of the trachea soon leads to death, but the tracheal calibre may be astonishingly reduced without killing the patient.

Case 1

A woman of thirty-seven, seen with Dr. P. K. Brown in 1920, had had a tuberculous pneumonia twelve years ago, and a year later "asthma," increasing with exertion. For the last three months she had had severe dyspnoea, wheezing, stridor and strangling fits, mainly at night. The X-ray revealed an apparent interruption in the course of the trachea with a widening of the lumen below. The thoracic viscera were displaced markedly to the left. Bronchoscopy revealed a tracheal obstruction at the level of the second sternochondral junction. Mediastinotomy disclosed no outward pressure, save pressure of the aorta which pushed the trachea to the right. The patient died. At

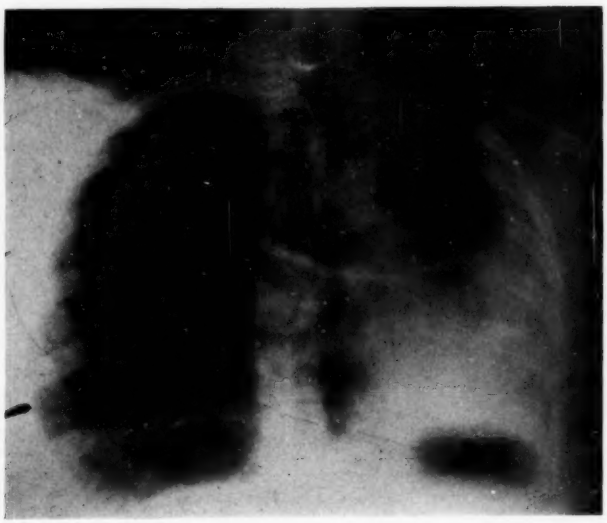
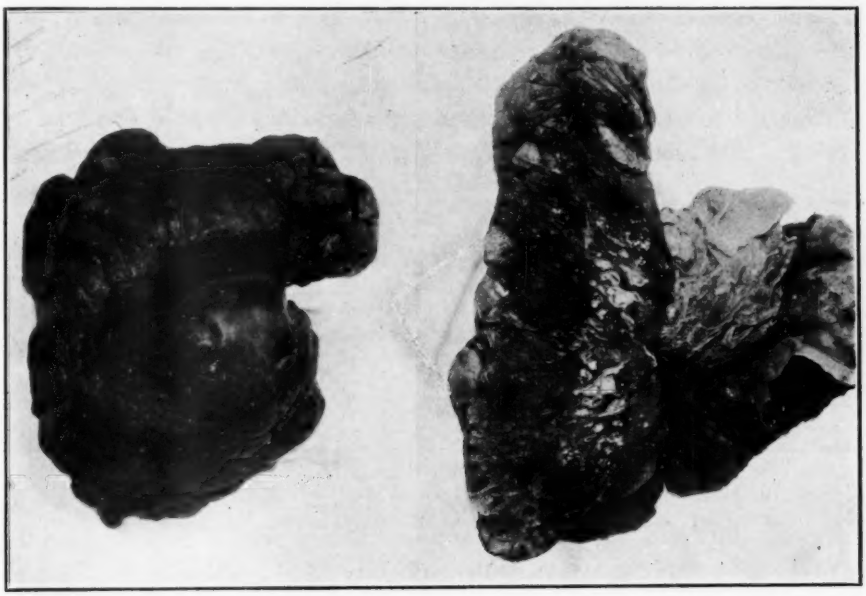


FIG. 8. Case 1. Narrowing of tracheal lumen at its middle. Contraction of left chest with huge cavitation of upper lobe and atelectasis of lower lobe. (Tuberculosis of the trachea).

autopsy the tracheal mucosa at the crossing of the innominate artery was found to be red and pitted, and the tracheal wall so thick that the lumen of the trachea barely admitted a lead-pencil. Dr. Ophüls reported a marked circular stenosis of the lower end of the trachea and dilatation above and below. There was a circular superficial irregular ulceration and induration of the tracheal wall for some distance on both sides of the ulcer. The right lung was emphysematous and the left lung completely collapsed. Visceral and parietal pleura was greatly thickened on the left side. Sections of the trachea showed much newly formed dense fibrous tissue, with areas of round-cell infiltration and shallow ulceration on the surface. In several places were groups of tubercles,

consisting of nodules of epithelioid cells with large multinuclear giant cells of Langhans type. There was marked fibrous thickening of the pleura without signs of tuberculosis. A smear from the left bronchus showed a moderate number of tubercle bacilli and no other bacteria. The microscopic diagnosis read: Tuberculosis of the trachea.

In partial obstruction the distal lung, from reasons which will be discussed presently, is emphysematous and its volume is increased. Simi-



a b

FIG. 9.[3] Case 17. Central chalicosis with diffuse obliterative bronchiolitis and fibrous tuberculosis. a. View from above showing huge emphysema bubbles. b. Cross-section: central peribronchial sclerosis and diffuse peripheral emphysema. Some large emphysematous bullae are cut open.

larly, lungs distal to obstruction at the tracheobronchial bifurcation, which affects both bronchial trees, are emphysematous. A more or less diffuse stenosing, but not completely obliterative bronchiolitis, also produces emphysema and an increase in lung-volume (figure 9).

Tuberculous stenosis may affect any portion of the bronchial tree. The major bronchi are frequently occluded by external pressure. Ex-

[3] Figs. 9a, 9b, 10, 29, 30, 31, 32, 41, 42a, 42b, 43, 44, 45, 46, 49a, 49b, 50 and 51 are reproduced from *Bronchial Stenosis*, L. Eloesser, Journal of Thoracic Surgery, 1931, 1932, i.

ternal pressure may also block the lobar bronchi, but ulcerative or hyperplastic tuberculomata, or peribronchial sclerosis are more often the underlying obstructive agents at this level.

If the lumina of the *lobar bronchi* are totally obstructed, air is absorbed from the occluded lobe, the lobe collapses and finally carnifies and shrinks, unless it contains purulent secretions, which when they are bottled up distal to an obstruction produce abscesses. Atelectasis fails to follow if the obstruction lies more distally, for, as Van Allen (7) has shown, there are anastomoses between the distal air-passages, so that the air can pass into a blocked territory from an unblocked one.

Space is wanting to enter into detailed discussion of the disturbances of function consequent upon obstruction at various levels. These have been discussed more fully elsewhere (8). It may, however, not be amiss

FIG. 10. Respiratory movements in tracheal stenosis. After exercise inspiration is more forceful; there is no longer a pause after inspiration.

to recall that, when breathing is mechanically interfered with, inspiration is at first prolonged and made deeper and more forceful, while expiration is comparatively unchanged, the difficulty being compensated for by prolonging and strengthening the intake. It is easy to see why. Nature has so adjusted our respiratory mechanism that the usual demand for increased oxygen supply, such as violent exercise, is met by an increase of intake, there being no reason for an increase of output. Obstruction to intake calls forth the same response; that is, inspiration is prolonged and strengthened.

This is the more remarkable because the inspiratory musculature is not nearly so forceful as the expiratory one: we can blow, cough or strain much more forcefully than we can suck. If the equilibrium between the need for oxygen and the possibility of getting it is still further upset: if the obstruction is increased, or the demand for oxygen is increased, either

by exercise or circulatory failure, then the compensating mechanism becomes insufficient. Inspiration is no longer deeper, slower and more forceful; respiration becomes more rapid, shallower and more ineffective, and death occurs unless help is rapidly possible. The disturbance of physiology that I have just tried to describe corresponds to two of the three stages of dyspnoea described by Gerhardt (9): namely, the stage of inspiratory dyspnoea, that is, the compensated stage, and the suffocative stage, that is, the decompensated one.

As a consequence of deep and prolonged inspiration and unchanged expiration, air is entrapped in the lung whenever an obstruction equally impairs intake and output of air; that is, the residual air is increased and an increase of lung-volume (*volumen auctum*), emphysema results. These changes have been repeatedly demonstrated experimentally, in models and in patients (Thornton & Pratt) (10).

It is the *signs*, dependent upon the changes in structure and function, that especially interest phthisiologists; they can be so accurately deduced and predicted that their interpretation offers a fascinating exercise for clinical ingenuity.

SYMPTOMS

The *symptoms of stenosis* are characteristic when the upper air-passages, the trachea or the bifurcation are obstructed. Dyspnoea then will often be extreme, there will be an audible respiratory stridor, and the patient may complain of suffocation on the least exertion. In the compensated stage breathing is slow, inspiration much prolonged, and expiration comparatively unchanged. In unilateral stenosis patients may complain of pain, pleurisy, or a pulling sensation in the affected side of the chest. The symptoms of low-lying obstruction are referable mainly to complications, to retention of purulent secretions with toxicity and fever. Occasionally there may be pain or a pulling sensation over the area occupied by a shrunken lobe.

Often symptoms are caused not so much by the stenosis itself as by its anatomical sequels, especially deformity of the trachea and the mediastinal viscera. A troublesome, dry, barking, irritative cough may arise from pull on the trachea, or asthmatic wheezing from distortion of the bronchi; at times sticky noises are produced by breathing.

SIGNS AND DIAGNOSIS

The *signs*, much more than the symptoms, are definite and characteristic. To begin at the top: *Partial obstruction of the trachea and partial*

obstruction at the bifurcation affecting both bronchi simultaneously (for complete obstruction at these levels leads to death in a few moments) cause dyspnoea, more or less intense, with inspiratory stridor often audible at a distance. The dyspnoea strangely enough is often more distressing to the onlooker than to the patient. It is strange how many patients will lie gasping for air and answer inquiries with "Oh no, I'm not much out of breath." They breathe with their auxiliary muscles; the intercostal and the supraclavicular spaces retract on inspiration and the veins of the neck fill and empty with each breath. The larynx moves far up and down. Gerhardt (9) says it does not. He states that in subglottic obstruction it remains more or less stationary in spite of intense dyspnoea, and explains its immobility by the fact that the air-pressure during inspiration rests not on it, but below it. However, being interested in this phenomenon I have paid attention to it and have seen the larynx make excursions of over 2 cm. in a case of low obstruction. It seems to me not unreasonable that the larynx should move even in low tracheal obstructions, for the trachea and larynx are so intimately attached that it is scarcely possible that the one should move without the other. In spite of the inspiratory stridor and the retracted intercostal spaces, the thorax is likely to be barrel-shaped. The breath-sounds may be diminished. The X-ray may give evidence of the emphysema; it may in a clear negative also show the trachea itself, deformed or compressed. The trachea and major bronchi are especially likely to be clearly visible if they are surrounded by enlarged lymph nodes or a peritracheal infiltrate which brings out the contrast between the outline of the air-filled trachea and the surrounding shadow. Indirect mirror laryngoscopy will not infrequently reveal the stenosis if it lies in the upper trachea; if not, the direct vision tracheoscope will not only reveal it but often allow treatment with dilators and bougies and biopsy. The stenosis may appear as a thickened mucosa which bulges into the mouth of the instrument, or the trachea may be scarry, narrow and deformed and admit only a small tube. At the bifurcation, especially, cheesy necrotic ulcers occur, partly from the breaking through of a caseous lymph node, partly from tuberculous ulceration of the wall itself. Pieces of necrotic lymph nodes, mentioned as being frequently encountered in children, may be seen and removed.

Case 2

R. D.: A baby of nine months of age was admitted to the San Francisco Hospital on February 8, 1929, with a history of bilateral tuberculous otitis media

of ten days' duration. The left cervical lymph nodes were enlarged. The entire left side of the chest was somewhat dull and the breath-sounds here were harsh. Films, taken February 15, showed the left chest to be obscured by a homogeneous shadow. By November a tuberculous peritonitis had developed, together with a Pott's disease of the spine. In May of 1930 the baby developed both an inspiratory and expiratory stridor. Laryngoscopy revealed nothing abnormal in the epiglottis, cords or arytenoids. The difficulty in breathing increased and the child's respirations varied from twenty-five to thirty per minute. At inspiration there was a loud inspiratory stridor, with intense retraction of the chest, so that during inspiration the ensiform was drawn back almost to the spine. The larynx did not descend on inspiration. Breath-sounds were audible though weak, and were heard equally over both sides of the chest. Inspiration and expiration were about equal in length, but the child paused at the end of inspiration. In view of the laryngoscopic findings the diagnosis was made of a tracheal compression just below the larynx, probably due to a peritracheal lymphadenitis. *Films* taken at Stanford Hospital by Dr. Chamberlain were reported as follows: There is no enlargement of the thymus. The difficulty with the child's breathing is due to a narrowing of the upper end of the trachea. A very narrow negative shadow, which is all that is left of the tracheal shadow, is pushed forward away from the front of the spine and is encroached upon from in front.

An effort was made to intubate the patient without success. During an attempt at bronchoscopy he became very cyanotic, so that tracheotomy was done. Thereupon the respiratory difficulty was relieved, but the child died three days later. At autopsy there was an interstitial emphysema of the anterior mediastinum. Just below the inferior border of the thyroid cartilage, attached to the arch of the cricoid cartilage and lying along the lateral parts of the *Conus elasticus*, was a large pea-shaped solitary tubercle, measuring approximately 8 x 8 x 8 mm. This left a narrow longitudinal slit, 1–2 mm. wide, along the dorsal part of the cricoid, continuous with the median notch of the cricoid lamina. There was also a tuberculous abscess of the thyroid gland.

STENOSIS OF A MAJOR BRONCHUS

Of major interest and importance to phthisiologists are the unilateral and unilobar stenoses. They are of such frequency that it is difficult to see how they could so long have escaped detection. Incomplete obstruction of the lumen of a major bronchus may, according to its degree, lead to more or less emphysema and dilatation of the obstructed side, for reasons set forth above. It is more difficult to detect than more or less complete obstruction, the signs of which are quite definite. The blocked lung is airless and shrunken. The hemithorax, in so far as its

constituent parts are movable, is contracted. The ribs are contracted; they lie with their transverse diameter in a more horizontal plane: the intercostal spaces are narrow, the mediastinum and the heart are drawn to the affected side and the diaphragm is raised. Pressure in the pleural cavity, if the pleural space has not been obliterated, is much diminished. Respiratory movement of the hemithorax is much diminished. Half of the chest may even stand quite still. Percussion gives a perfectly flat

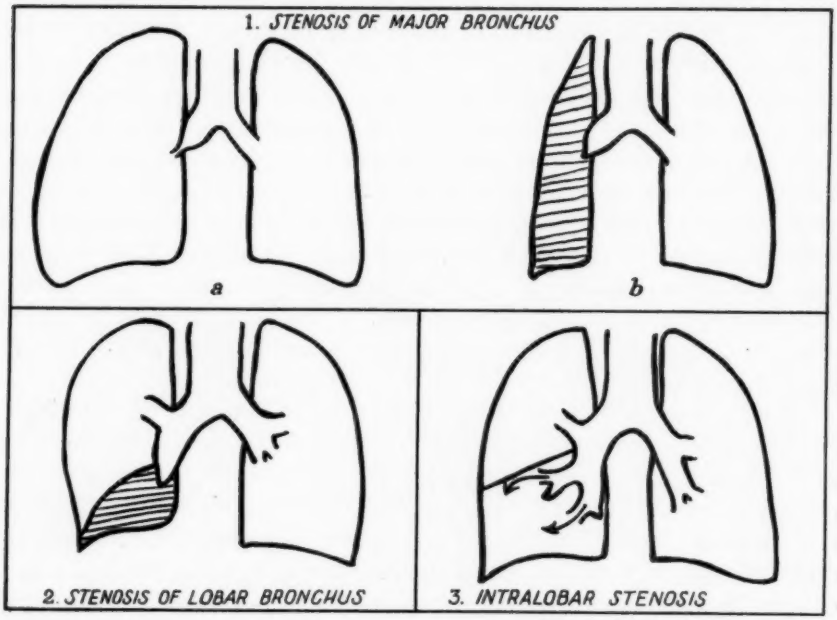


FIG. 11. 1. Stenosis of major bronchus.
a. Incomplete. Emphysema and dilatation of lung.
b. Complete. Atelectasis and contraction of lung.
2. Lobar stenosis (complete). Contraction and atelectasis.
3. Intralobar stenosis. No contraction or atelectasis (interalveolar communication).

solid note, and if the stenosis involves the whole major bronchus the whole chest from top to bottom is flat. Breath-sounds over the affected side are absent or much diminished, so that one can readily see how such a blocked, airless lung may be mistaken for a chest full of fluid.

The X-ray demonstrates, as may be expected, the airless lung, a massive unilateral density occupying and contracting the hemithorax. It shows the horizontal ribs, the projection of which is narrower than on the

other side; it shows the narrow intercostal spaces and the ribs tightly squeezed together; it shows the retracted heart, the retracted mediastinum and the raised, more or less immobile diaphragm. The homogeneous density and retraction of the chest can scarcely be mistaken for a fluid shadow. Jacobson (11) has shown in recent stenosis in which the mediastinum and diaphragm are still mobile that coughing or straining decreases the deviation and inspiratory effort increases it; this phenomenon can best be seen in the fluoroscope. The reason for it is clear;

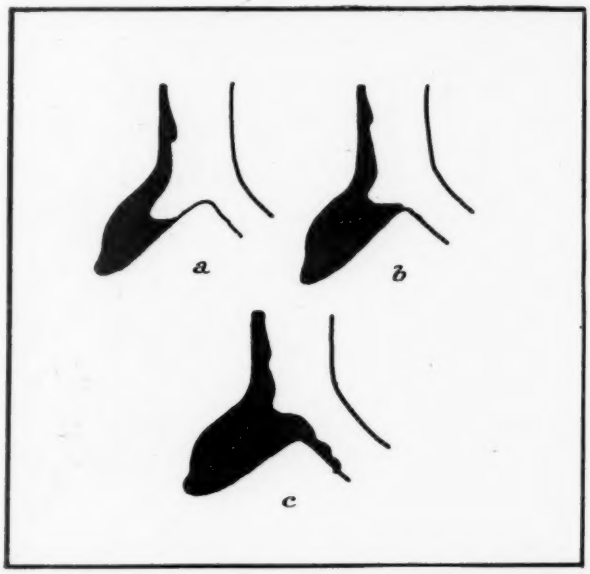


FIG. 12. Lipiodol injection in stenosis: a. Flows into obstructed bronchus. b. Fills bronchus. c. Flows over into other side.

inspiration increases the tug on the airless lobe and the mediastinum follows. Increase of intrathoracic pressure decreases the pull on the mediastinum. If, dissatisfied with this evidence one inclines to venture an injection of opaque oil (which in pulmonary tuberculosis is not without risk), the oil will refuse to enter the obstructed tree. By inclining the patient toward the obstructed side one may watch it flow down to the stenosis, puddle, rise to the level of the tracheal bifurcation and then flow over into the contralateral lung. At times a thin stream will penetrate the site of stenosis and trickle slowly through. The bronchoscope finally caps the diagnosis. One sees the tracheal bifurcation, the carina pulled

aside or twisted or both; without inclining the instrument to one side or the other, one can look straight down the open side, but to see the obstructed bronchus, one may have to push the tube strongly to the right or left. The tracheal and bronchial rings at the entrance to the blocked side may be obliterated, their corrugations covered by thickened or reddened mucosa or flattened by scarry contraction. One sees or comes up against the stenosis: it presents a funnel-shaped opening covered with pale and

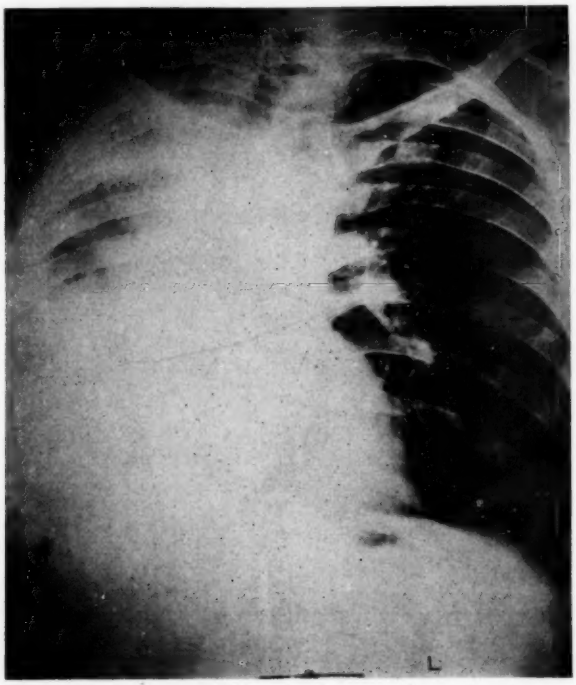


FIG. 13. Case 3. Marked contraction of right chest. Airless right lung. Heart, trachea and mediastinum displaced to right.

scarry mucosa, or perhaps an ulcerated cheesy white area, which bleeds easily. Through the narrow funnel a bougie may be inserted, so that the stricture may not only be seen but felt. The most skeptical will now no longer remain in doubt. On withdrawing the bougie a thin, worm-like stream of viscid pus may follow.

Cases 3 to 6

3: A Dalmatian gardener, miner and cement-worker was referred by Dr. Knorp of San Mateo on October 6, 1930. In 1909 he had had a pleurisy and

was very sick for a year and a half, but afterward gained much weight. In 1918 he had influenza and has been dyspnoeic ever since. He had coughed for the past fifteen years.

Both tops of the chest moved, but the right base lagged on respiration. The right base was flat and breath-sounds were absent, but one heard coarse râles, squeaks and bubbling noises over this area. Over the right apex the breath-sounds were diminished. The heart lay almost entirely in the right side of the chest and the mediastinum was moved far to the right. The left side was free. The fingers were clubbed and the man was very short of breath.

FIG. 14. Case 4. Stenosis of left major bronchus. Left side of chest is contracted and airless, except for cavity at left apex.

The shrinkage of the right chest, the deviation of the trachea and the heart, and the airlessness of the right lung were visible in the X-ray (figure 13).

The diagnosis of tuberculous stenosis of the right major bronchus was confirmed by bronchoscopy. The left major bronchus was seen to make a straight line with the trachea. Its walls were normal and its mucosa was pale. The carina deviated so that its anterior edge was to the right and its posterior one to the left. It was necessary to push the tube far to the left in order to see down the right major bronchus. One now saw that its mucosa was thickened, red and inflamed, so that the cartilaginous rings were indiscernible. Upon lifting the tube far to the front one began to see a lumen. This was full of a viscid secretion, whereas no secretion came from the left side.

Diagnosis: Bronchial stenosis and deformity of the right bronchial tree, tuberculous. The bronchoscopy was immediately followed by an avulsion of the right phrenic nerve.

4: M. R. T.: Twenty five years old; was seen on December 29, 1931, with Dr. Thomas O'Connor of the Bret Harte Sanatorium. She had been admitted there on July 9, 1928. On admission there was a large cavity at the left top, for which pneumothorax had been induced. The air-space was gradually lost.

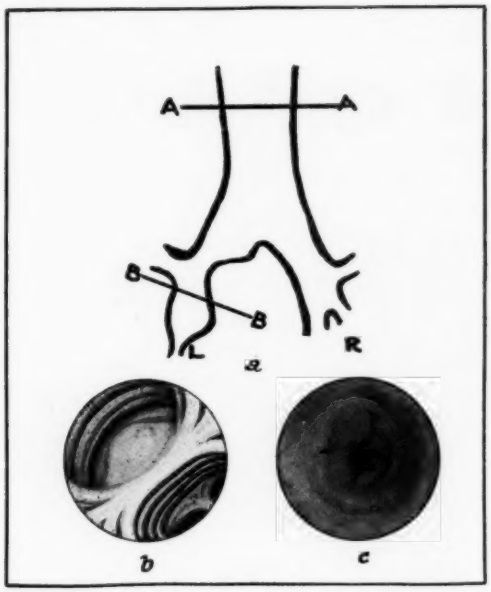


FIG. 15. Case 4. a. Diagram of bronchial tree showing bulge of medial wall of left major bronchus and constriction of bronchus below this point. b. Bronchoscopic view at level AA, showing bifurcation and bulging wall of left bronchus. The bulging wall obstructs the view of the stenosis until the bronchoscope reaches the level BB. c. Bronchoscopic view of stenosis with bronchoscope at BB.

When seen, the whole left side was dull; no breath-sounds were to be heard, except at the left base, where many crepitations were audible. Bronchoscopy was done April 19, 1932. The right bronchial tree was normal, but the lumen of the left major bronchus was occluded by a projection of its medial wall. This bulged forward so that it occupied almost the entire lumen of the bronchoscope. After swinging the instrument as far as one could to the left, one saw, some 3 cm. below the bifurcation of the trachea, a triangular opening not over 2 mm. wide, the lips of which opened on inspiration and closed on expiration. The edges of this stenosis were thickened and at this area the normal corrugations of the bronchial cartilages were lost.

Although bronchoscopy in this patient revealed an inspiratory and expiratory closure of the stenosis, so that one might assume that the patient had a valvular stenosis which would produce a dilatation rather than a collapse of the lung, it is doubtful whether this valve action existed under normal conditions. The dilatation of the bronchial tree produced by insertion of the rigid metal tube stretches the walls of the collapsed and deformed bronchi, so that it is not possible to deduce from the action seen during bronchoscopy the action of the normal respiratory process.

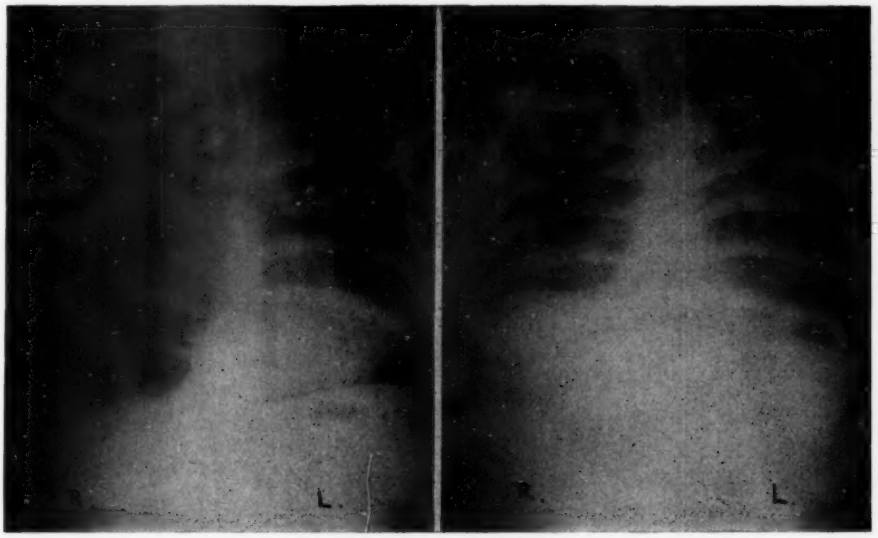


FIG. 16 FIG. 17

FIG. 16. Case 5. Stenosis of left major bronchus. Inspiration. Marked displacement of heart and mediastinum to left. Gray left chest.

FIG. 17. Case 5. Same patient; expiration. Displacement of heart and mediastinum less marked. Disparity in density of two sides of chest less marked.

5: J. S.: A Hungarian steel-worker, forty-four years of age, was referred, February 27, through the kindness of Dr. Thoren of Weimar Sanatorium. In October, 1930, he developed a pain in his left chest and began to expectorate. Tubercle bacilli were found in his sputum and he was admitted to Weimar Sanatorium. He was afebrile and gained much weight, but continued to expectorate 2–3 oz of consistently positive sputum. An attempt at pneumothorax was unsuccessful. Although the Wassermann reaction was negative there was a history of chancre in 1919; there were no clinical signs of syphilis.

The left side of the chest lagged and was dull. Breath-sounds over the left side were diminished in intensity, but there was an amphoric note under the

left clavicle. There were numerous râles all over the left chest. The right chest was clear. Films of the chest revealed displacement of the heart and mediastinum to the left, with some small cavities under the apex. The right pleura had a wide excursion, but the left moved very little. The mediastinum moved to the left on inspiration and to the right on expiration, but there was no paradoxical movement of the diaphragm. A film taken in inspiration and another in expiration showed that inspiration pulled the mediastinum and trachea to the left (figures 16 & 17). The right lung-field was clear.

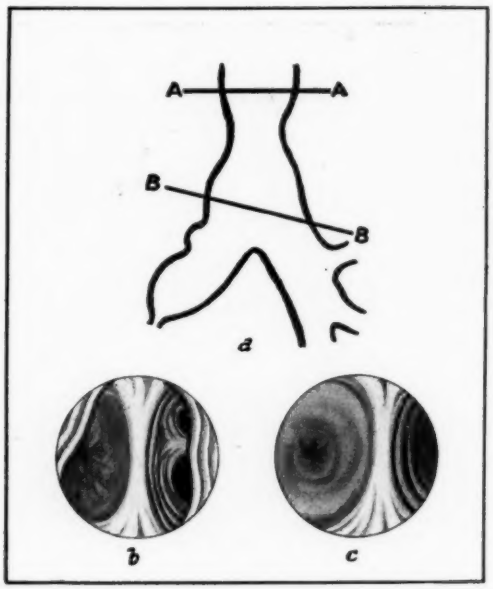


FIG. 18. Case 5. Same patient. a. Diagram of tracheobronchial tree. b. View at section AA showing deformity of lateral tracheal walls. c. View at section BB. Bronchoscope deflected to right, looking down at stricture of left bronchus; a small segment of right normal bronchus appears in the field.

There was a moderate increase in density of the left lung. Several renewed attempts at pneumothorax succeeded in introducing air.

Bronchoscopy was done on April 13, 1933. The carina was seen to be sharp and in the midline, but both the right and left lateral tracheal walls encroached on the lumen of the instrument, so that the configuration of the trachea was much like that of the *Rima glottidis*. The right bronchial tree was normal. The left bronchial tree was injected and the cartilaginous rings were not seen through the swollen mucosa. Nowhere in the left major bronchus did the lumen appear. A bougie entered the bottom of a funnel, which represented the left major bronchus. The bougie could be inserted for a centimetre or so

into the funnel, but not further. No ulceration was seen (figure 18). *Diagnosis* was made of a tuberculous sclerotic nonulcerative stenosis of the left major bronchus. Nine examinations of sputum at the San Francisco Hospital failed to reveal tubercle bacilli, nor did a direct smear from the left bronchial tree reveal them. Were it not that they were repeatedly found at Weimar Sanatorium during the early course of this man's disease, I should have thought his stenosis was not unlikely syphilitic.

6: D. F.: A Chinese girl of twenty-six was admitted to the San Francisco Hospital from Arequipa Sanatorium, December 13, 1931. She had entered

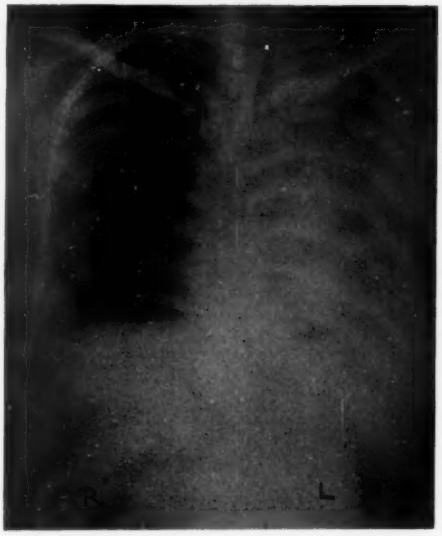


FIG. 19. Case 6. Stenosis of left major bronchus. Contracted and airless left hemithorax.

Arequipa a year previously. For the first few months she did well, but then had repeated small haemorrhages, which have persisted, together with some dyspnoea on exertion. There was a persistent lag and retraction of the left chest, with deviation of the heart and trachea to the left. The entire left side was dull and almost flat. Breath-sounds over the left side were much diminished and there was much moisture heard after cough. The sputum varied from 40 to 85 cc. per day. Miss F. was afebrile, except when she bled, after which the temperature reached 102–103°. Phrenicectomy was done in April, 1933, since when there have been no haemorrhages. Her vital capacity, recumbent, was 700 cc. Bronchoscopy was done in January, 1932. A sharp-

edged carina deviated from the left above to the right below. On the medial side of the left main bronchus, 1–2 mm. below the carina, lay a white scar. The left main bronchus made a fairly straight line with the trachea at first, then deviated sharply to the left. Its mucosa bled easily when touched. The left lung was full of secretion. About 2 cm. below the bifurcation the lumen was narrowed to a small transverse slit, which opened when the tube was passed through it, but immediately closed again when it was withdrawn. The mucosa at this site was much injected, but no ulceration was to be seen (figure 20).

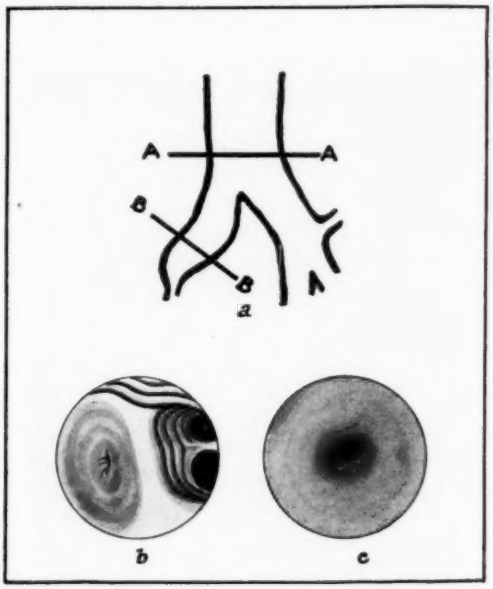


FIG. 20. Case 6. Same patient. a. Diagram of tracheobronchial tree showing deflection of left major bronchus and left bronchial stenosis. b. View at section AA, showing torsion of carina and left bronchial stenosis; small part of right bronchial tree appears in field. c. View at BB. Stenotic left bronchus.

Diagnosis: Stenosis of the left major bronchus, 2 cm. beyond the bifurcation (possibly through external pressure,—encroachment of tuberculous lymph nodes?).

Stenoses which intermittently open and close are most puzzling. Nontuberculous are perhaps more frequent than tuberculous ones. The signs vary, sometimes from day to day, with surprising rapidity. One examiner will report that the chest is completely flat and the breath-sounds inaudible, so that, suspecting fluid, he introduced a needle and

got a dry tap. The next day another examiner finds the chest clear. He calls the first man, who reëxamines and can scarcely trust his own ears. X-rays taken even a few days apart may corroborate the sudden change. This remarkable change is not so likely to occur in tuberculous stenoses, but is not infrequent with nontuberculous ones. Clinical symptoms, fever, toxicity, dyspnoea abate when the stenosis is open and soon reappear when it is closed, if infectious secretions are confined in the lung.

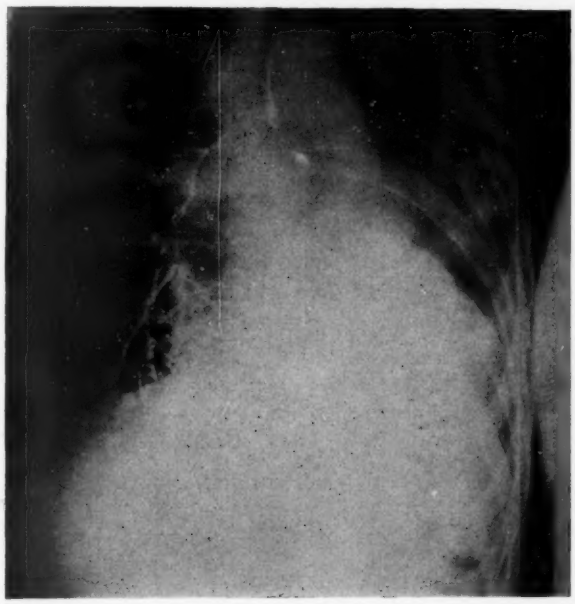


FIG. 21. Lipiodol injection. Stenosis of left major bronchus. A spot of lipiodol seen filling origin of left major bronchus, the remainder has spilled over into the right base (case 7).

Case 7

Chronic intermittent bronchial stenosis, probably syphilitic: A Swedish miner and lumberman of twenty-eight was admitted to the San Francisco Hospital on November 22, 1925. On leaving Alaska in 1922 he had begun to complain of a dry, unproductive cough, shortness of breath and pain in the left chest. He had spent all but four months of the years 1922–1925 in hospital. He had two attacks of fever, attributed to "pneumonia," in which his cough was productive; otherwise he had brought up nothing.

Prior to admission to the San Francisco Hospital he had worked for a few months, but had quit ten days before on account of chills, fever, and uncontrollable paroxysms of cough with very little expectoration.

On examination, the left side of the chest was much contracted and dull, especially posteriorly and in the axilla. Over the left apex the breath-sounds were cavernous. There were râles over both lungs. The heart was retracted far to the left, the apex being felt in the fourth intercostal space just behind the anterior axillary line. Repeated puncture of the chest brought forth no fluid. X-rays of December 17, 1925 were reported as showing a thickened left pleura, especially at the left base, with wide and dense hilar shadows and numerous calcified hilum lymph nodes. Both apices and the area of the first right intercostal space were a little mottled.

Lipiodol injected into the trachea puddled in the left main bronchus about 2 cm. beyond the bifurcation and, as more was injected, filled the bronchus to the bifurcation and spilled over into the right side. Films showed that a little lipiodol had found its way through the stenosis and entered the left lower lobe (figure 21). Bronchoscopy by Dr. Graham revealed a normal right bronchial tree and a blocking of the left major bronchus by a firm fibrous mass which did not bleed when touched. Exploratory thoracotomy was performed April 1, 1926, after preliminary pneumothorax. The right hilum was surrounded by enlarged lymph nodes. Manipulation of these nodes provoked an uncontrollable cough which made further exploration impossible. The chest was closed. The patient was considerably shocked by the operation, but recovered and was relieved of his dyspnoea. Bronchoscopy a month later showed that the obstruction to the left bronchus had practically disappeared. The bronchoscope passed through the area which had formerly been stenotic, so that the smaller branches could be explored. The only abnormality noted was some congestion of the mucosa.

The man brought up from 30 to 55 cc. of purulent sputum daily. Seventeen examinations of this expectoration failed to show tubercle bacilli. The Wassermann reaction twice repeated was doubtfully positive.

The patient continued to improve and got about the ward with little dyspnoea. On April 14 the left lung field was still gray, but the trachea and the heart occupied almost normal positions; on May 26 and June 24 the lung was much better aerated (figures 22 to 25).

The man was discharged and went to work as a waiter in a lumber-camp. He reëntered hospital November 26, 1926. He had been somewhat out of breath, had coughed a little since his discharge, but had had no severe paroxysms and no fever up to five days ago when he was taken with chills and a temperature of 104°F. This lasted for two hours, when he coughed up a large amount of green sputum and the fever dropped to 101°F. It had risen to 103°F. since. The left chest was again dull, and the breath-sounds diminished or absent. Lipiodol injected into the bronchi again stopped at the site of stenosis, and bronchoscopy revealed a stenotic left bronchus with a very small opening from which pus exuded. The temperature dropped,

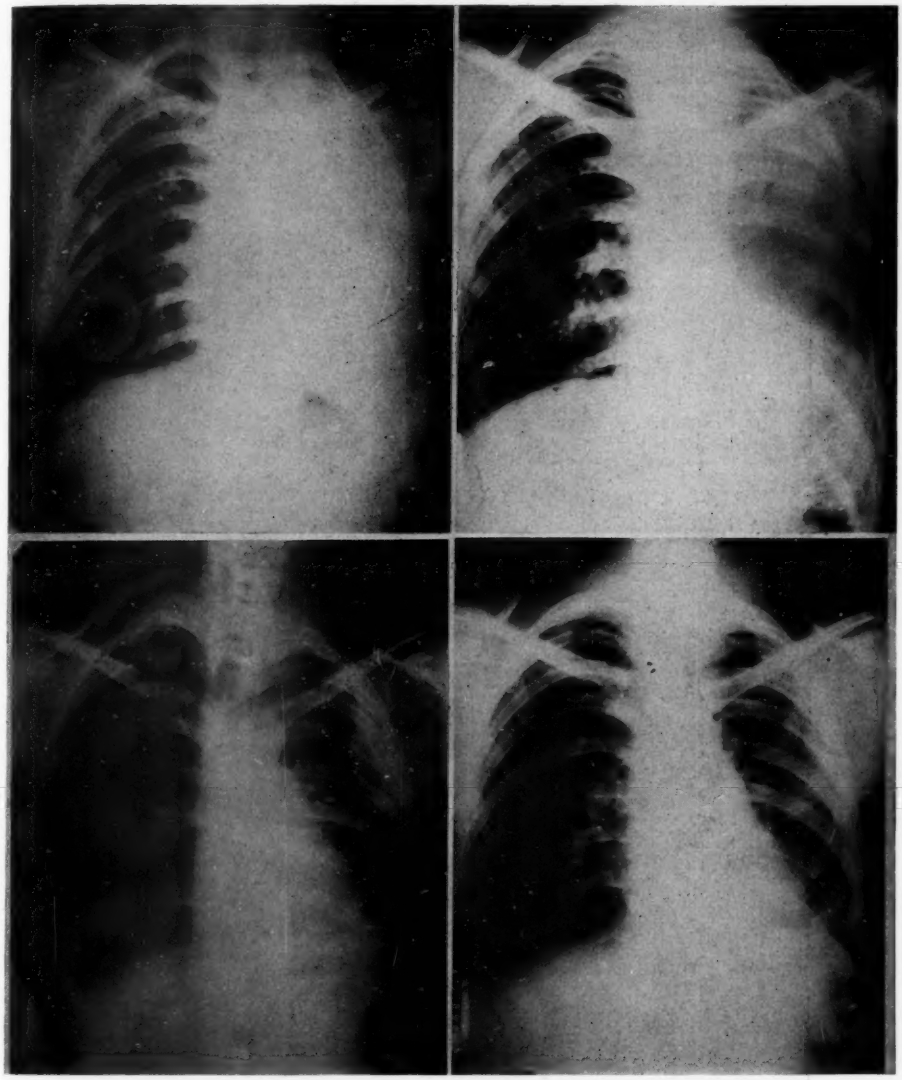


FIG. 22. Feb. 18, 1926. Airless left chest: marked contraction
FIG. 23. May 7, 1926. Beginning aeration
FIG. 24. May 25, 1926. Aeration progressive
FIG. 25. June 26, 1926. Aeration practically complete

but on November 30 rose again; the coughing-fits and dyspnoea grew more severe, the pulse was rapid, and over the left upper chest loud tubular breathing with bubbling râles could be heard. The man died on December 3, 1926.

At autopsy the next day the heart was found to lie almost entirely on the left side of the body; the right lung was emphysematous and projected a little beyond the midline. The left pleura was obliterated by strong adhesions.

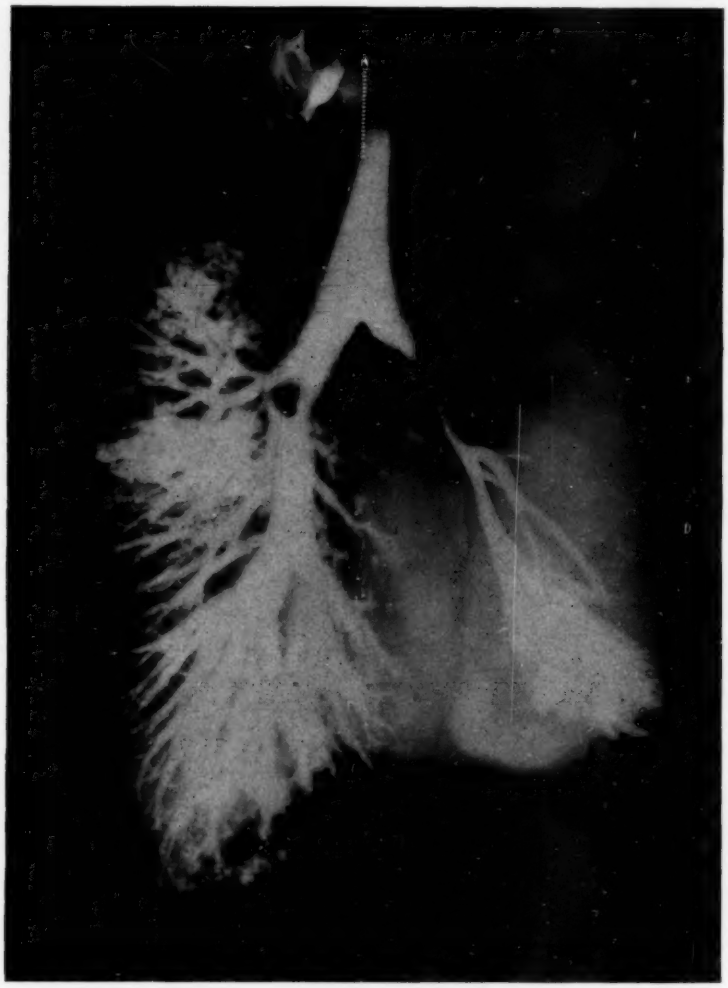


FIG. 26. Case 7. Autopsy specimen injected with barium-gelatin. Stenosis of left major bronchus; peripheral bronchiectasis left lower lobe.

There was a narrow stenosis of the left main bronchus, 2–3 mm. in diameter (figure 26). At this point the bronchial wall was 4 mm. thick, as against 2 mm. in the unaffected portion. The mucosa was smooth, gray and much

congested; at the narrowest portion it was somewhat scarred. There was no induration of the tissues around the stenosis, but right close to it lay some soft lymph nodes, the largest 2.5 cm. in diameter, some grayish-red, some light gray with light spots.

The *left pleura* was very thick, the *left lung* very small and its apex free from scars. The *bronchi* distal to the stenosis were dilated and filled with a dirty brown fluid. The bronchi of the upper lobe were also more or less dilated; the lung was dark red and almost solid. The *right lung* was very large, emphysematous; the posterior two-thirds of the lower lobe and the posterior half of the upper lobe were consolidated. The middle lobe was free; the bronchi were not dilated.

The *heart* was of normal size; the right half was dilated. Sections of the *peribronchial lymph nodes* revealed marked congestion and hyperplasia and slight capsular thickening. There was no evidence of tuberculosis.

Diagnosis was made of stenosis of the left major bronchus, bronchiectasis and terminal pneumonia.

DIFFERENTIAL DIAGNOSIS

Fluid and stenosis

Diagnosis is not difficult if the possibility of stenosis is considered. Stenosis, like all processes that deprive the lung of air, leads to a massive dulness over the affected chest, with absence of breath-sounds. These signs are also those of fluid. It may be pardonable to point out again that fluid occupies more than normal space and the shrunken lung less; so that with the one the chest bulges and the mediastinum is pushed away and with the other the chest shrinks and the mediastinum is pulled toward the bad side. Fluid ordinarily leaves a resonant area at the top of the chest; stenosis does not. The X-ray can demonstrate a shifting fluid-level and localize the position of the mediastinum even more accurately than percussion. The aspirating needle will finally clear the diagnosis. Stenosis and fluid, unless they are both present, are ordinarily not difficult to tell apart.

Differentiation of diffuse fibrosis and stenosis

Much more difficult to differentiate by clinical means,—impossible at times, I think,—is the persistent diffuse fibrosis and atelectasis that one sees in lungs that have long been compressed by pneumothorax. Diffuse fibrosis and stenosis both give rise to clinical and radiographic appearances precisely similar. In both, half the chest is entirely dull or flat,

contracted, immobile, airless; in both, the X-ray demonstrates the airlessness by a uniform density and the contraction by mediastinal and cardiac and diaphragmatic and costal deviation. The reason for this similarity, the reason for the difficulty in diagnosis has been obscure,—to me at least,—but I think that it lies in the fact that both stenosis and continued external compression lead to the same result, namely, airlessness, and that airlessness and lack of function lead to fibrosis, and that fibrosis, whatever its cause, gives rise to the physical and radiographic phenomena enumerated above. For we know that as long as blood continues to circulate through the lung the air contained in it will be absorbed unless it can continually be replenished by fresh air; and whether this replenishment be prevented by shutting off the air-ways, or by externally preventing the lungs from moving, is immaterial; atelectasis will result.

One clinical sign, perhaps, may give a clue. It may be that the breath-sounds are absent or diminished in stenosis, and that in fibrotic, but not obstructed lungs (provided one can hear them through the many pleural squeaks and creaks), they are tubular and fairly loud. If this surmise can be corroborated consistently, then it should offer one clinical means of differentiation. However, if clinical examination and the X-ray leave the diagnosis undetermined two means are still open,—opaque oil will demonstrate a stenosis or its absence and so will the bronchoscope. If there is a question of tuberculosis of the contralateral lung, use of oil may be not without risk; bronchoscopy, if gently done, should be harmless and may be of considerable therapeutic benefit. In afebrile cases of questionable stenosis, bronchoscopy should be done.

Case 8

Miss Violet M.: Was admitted to the San Francisco Hospital for the first time on November 7, 1927. Her cough and sputum dated from 1925–1926. On admission there was found an extensive involvement of the left side of the chest, with a huge apical cavity some 4 in. in diameter. In the course of the next year a small effusion developed at the left base. Tubercle bacilli were found in the sputum. She remained in the hospital until 1930 being transferred in December, 1928, to the Health Farm. Her fever abated and gradually the whole left side became dense.

She was readmitted on January 23, 1931. There was consolidation of the left chest and a diagnosis was made of atelectasis of the left lung. Loud tubular breath-sounds were heard over the left top. At the left base the breath-sounds were diminished. The right side was unaffected. A pneumothorax

was induced and, upon introducing the needle, the negative pressure was found to be *minus 16*. This reading drew the fluid out of the manometer, wherefore further pressures could not be measured. Air was introduced every four or five days at negative pressures varying from minus 9 to minus 12.

The first bronchoscopy was done on March 4, 1931. Although a stenosis was expected the bronchoscope entered easily. The carina deviated from the right anteriorly to the left posteriorly. The bronchi of the 2nd and 3rd order at the base of the left lung could be visualized without trouble. There oozed from them continually a thick, viscid secretion. The diagnosis remained

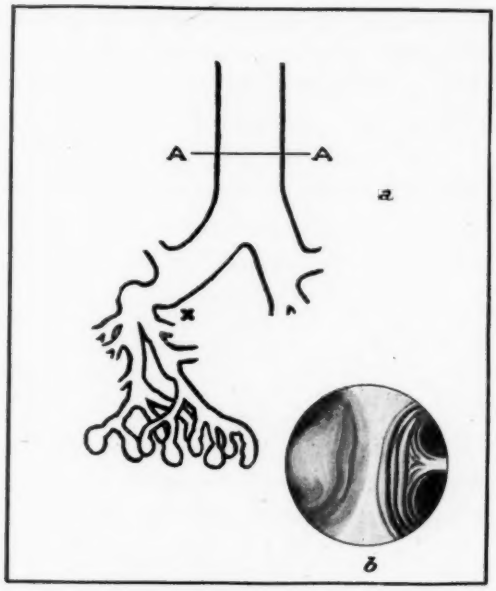


FIG. 27. Case 8. a. Diagram of bronchial tree showing how the distorted bronchial wall obstructs the view until the bronchoscope is swung around the curves of the bronchial tree. At X walls, viewed from above, cause apparent, but not real blocking of lumen. b. Carina with lumen at X appearing as a slit.

doubtful; for although no obstruction was found to the entry of the bronchoscope, the high negative pressure in the left chest, together with the evident airlessness of the left lung, made it likely that before entry of the instrument, at least, an obstruction to breathing had existed.

The patient was discharged from the hospital, but reported from time to time. She was increasingly dyspnoeic. Her pulse was increasingly rapid. Her respirations on even the slightest exertion reached 50 and the pulse 140. As before, breath-sounds were loud over the left top but decreased at the left base.

A second bronchoscopy was done June 20, 1933, and again demonstrated the deviation of the carina. The left bronchus made a straight line with the trachea. It lay unusually far backward. The upper left bronchial rings were visible, but not the lower ones. About 2 cm. below the bifurcation one saw a scarry thickened white mucosa. The path traversed by the bronchoscope constantly had before it a mucous membrane with no open lumen until this thickened place was passed.

The apparent obstruction was evidently due to kinks and distortion of the bronchial tree rather than to a narrowing, for the large tube encountered no difficulty in passing the devious course of the bronchus. After the scarry white area had been traversed, one saw red and thickened basal bronchi of the third order, which were full of a mucopurulent secretion. Diagnosis was made of bronchiectasis of the left base (figure 27). It is entirely possible that the bronchial tree may collapse when the rigid bronchoscope is not in place and that, in viewing it through the bronchoscope, one sees it under artificial conditions, which the instrument itself creates. A lipiodol filling would give the desired information.

TREATMENT

Whether or not to treat stenosis of a major bronchus with collapse has puzzled me often. No doubt many, many such stenoses have been so treated. No doubt many of them unwittingly and no doubt many of them with benefit. It is doubtful, however, whether more of them may not have been harmed; whether partially stenotic bronchi may not have been closed off entirely and whether some pulmonary suppurations, poorly drained through a partially stenotic bronchus, may not have been blocked entirely, to the harm of their bearers. It may, perhaps, be safe to say that collapse should be considered in total stenosis, if the patient is afebrile and not toxic and if the complaints are due not so much to the stenosis itself as to anatomical derangement of the thoracic viscera occasioned by the shrunken lung. In such patients pneumothorax, phrenic avulsion or thoracoplasty, will be of benefit.

STENOSIS OF A SINGLE-LOBE BRONCHUS

Stenosis of a single-lobe bronchus is no less frequent than stenosis of a major bronchus. Although bronchial carcinoma is a common cause of stenosis of a bronchus leading to a single lobe, tuberculous stenosis is not rare. The stenosis may be extramural, by pressure of hilar lymph nodes, or by the constriction of peribronchial infiltrates. It may be mural, through shrinking and sclerotic tuberculous changes in the bron-

chial wall (although such changes are more likely to be nontuberculous), and more often than in other situations it may be due to a caseating ulcerative bronchitis.

Even in the presence of tuberculosis, such sclerosing and deforming submucous and peribronchial infiltrates may be due to nontuberculous complications. Thus Schmorl (4) and Gey (5) have described a nontuberculous sclerosing process under the name of *Bronchitis deformans* and have thought that tuberculosis in the stenosed area was rather secondary than primary. Sergent, Benda (6) and other French authors have emphasized the rôle of syphilis in causing peribronchial sclerosis and have said that, in the presence of both syphilis and tuberculosis, it is syphilis that imprints its characteristics on the lesion. It would lead too far to discuss these questions of pathology in detail, especially as they have been extensively discussed elsewhere (8).

Stenosis of a single-lobe bronchus as such may cause no symptoms. There may be fever and toxic symptoms from retention of purulent secretion, or cough from the irritation of a stenotic lesion lying near the carina, or occasionally pleuritic pain and a localized sense of dragging, or a feeling as though the inhaled air failed to reach the involved part of the chest; again the underlying tubercular process may cause symptoms, but obliteration of a single lobe may not make itself felt either anatomically or functionally.

Signs and diagnosis of lobar stenosis

Signs of lobar stenosis, however, are characteristic. Localized retraction of the chest, either over a lower or an upper lobe, with local retraction of the ribs and the intercostal spaces, localized immobility of a portion of one side of the chest, either lower or upper, deviation of the trachea from the midline at the sternal notch without deviation of the heart, or *vice versa*, are sufficient to arouse suspicion of shrinkage of a single lobe.

A dull percussion note may accompany these signs, although dulness is elusive and deceptive. The shrunken lobe may be very small and covered by its neighbor. Partly for the same reason, but also when the airless lobe seems not greatly diminished in size, changes in breath-sounds are doubtful. Absence or diminution of breath-sounds over the stenotic area is not constant,—often the breath-sounds are fairly loud and tubular. An infectious pleurisy over the airless lobe may cause the overlying intercostal spaces to be tender to pressure.

The X-ray again corroborates suspicion; it demonstrates the localized retraction of the chest-wall, the narrow intercostal spaces, mediastinal and tracheal deviation, at times rise and impaired mobility of the diaphragm. The films, however, may need careful study, for the

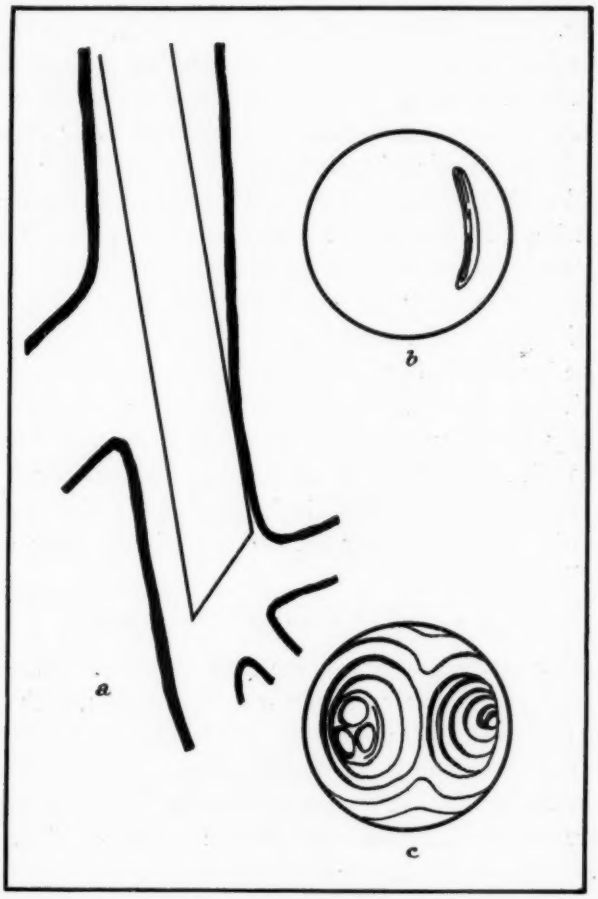


FIG. 28. Diagram of bronchoscopy showing why the upper lobe bronchus appears as a crescentic slit (b), but the lower lobe bronchi appear as round tubes (c).

shrunken lobe may be so small, or so displaced, or both, that it may be difficult to recognize. Jacobson (11) already noted in his first observation that if one whole lung was blocked the mediastinum deviated toward the blocked side on inspiration; if, however, the sponge with which he produced his stenosis was pushed further down, no such deviation took

place. This again corroborates Van Allen's (7) demonstration of an intralobar connection between the smaller bronchi, which allows air to pass from one smaller bronchus to another, and thus to circumvent an intralobar stenosis. Text-books of radiology give insufficient detail.

Opaque oil, if one cares to risk it, may or may not give definite information. Filling an upper-lobe bronchus is so uncertain that, if it remains unfilled, a suspicion that the technique was at fault, rather than that the bronchus was actually blocked, may be hard to allay. Stenosis of both lower bronchi and of the right middle bronchus should be definitely demonstrable with opaque media. In upper-lobe stenosis even the bronchoscope may forsake us. For, the mouth of the middle and lower bronchi can be seen and a stenosis demonstrated bronchoscopically, but the mouth of an upper-lobe bronchus can be seen only from the side at best. It usually presents itself as a narrow crescent, down which, or up which rather, it is impossible to look (figure 28). What lies beyond the very mouth, and indeed the shape of the mouth itself, are not discernible. Furthermore, and for the same reasons, the upper lobe bronchus cannot be entered with a bougie, unless one is lucky enough to poke one around a corner.

So that while diagnosis of lower-lobe stenosis is usually not difficult, an upper-lobe stenosis may be impossible to ascertain.

Differential diagnosis

Differentiation from a caseous lobar pneumonia should be easy in aseptic stenosis: with the one patients are very sick, with the other not. However, to distinguish a tuberculous lobar pneumonia from a stenosis complicated by retention of septic secretions, may be impossible,—often both coexist, the stenotic retention of tuberculous pus being the cause of the concomitant caseous pneumonia. Shrinkage of the stenotic lobe may be visible in an X-ray, while the caseous consolidated lobe should retain its original size. One will hesitate to resort to bronchography or to the bronchoscope in highly febrile toxic tuberculous patients,—but either, if used, will allow of differentiation in lesions of the lower lobe,—although, for reasons just stated, not in the upper lobe. A high white count will speak more for retention of septic secretion and a low one with mononucleosis for caseous pneumonia. If the stenosis is not permanent but intermittent, and if X-rays taken at short intervals show now a solid density, now a partially air-containing lobe, the diagnosis of stenosis is made and the suspicion of caseous pneumonia may be dismissed, for a caseous pneumonia does not vary from day to day.

Differentiation of chronic stenosis from chronic fibrosis, that is, chronic compression atelectasis, is usually difficult unless increased breath-sounds over the apex may speak for fibrosis; prolonged observation may show remission of obstruction with X-rays of the apex now airless, now air-containing; a successful filling with opaque oil may definitely exclude stenosis, but one hesitates to use oil in tuberculosis and attempts at filling the apex are so open to technical errors that failures are always doubtful.

What has been said of caseous pneumonia and fibrosis holds good largely also for tumor, except that in tumor the bronchoscope plays an all important rôle, and biopsy, if one can get a bit of the growth, dispels all doubt. Distant metastases, steady but slow progression and encroachment visible in the X-ray will help. However, here too diagnosis may require repeated and unrelaxing attention. Biopsy may fail to reach the tumor itself and remove but bits of inflamed bronchial wall; temporary remission of symptoms is not unknown in tumor and it must not be forgotten that tumor and tuberculosis may coexist.

Often enough the autopsy table will put an end to theorizing and speculation.

It may now be best to treat of the various lobes seriatim and to illustrate with instances. Although *stenosis of a single upper lobe* may be extremely difficult to diagnose, it is of all lobes the most important to phthisiologists. Differentiation between stenosing upper-lobe bronchial tumor, between upper-lobe bronchial tuberculosis and between a chronic tuberculous fibrosis of the upper lobe, just discussed, may be of much more than theoretical importance, for the one may demand opening the chest and the other contraindicate it: The following case may illustrate these difficulties.

Case 9

Tuberculous stenosis of right upper bronchus: A doctor's wife of fifty-three entered St. Joseph's Hospital in October, 1928, complaining of pain in the right chest and distressing paroxysms of cough, with a yellowish sputum which at times was offensive and often contained blood. She had had pleurisy with effusion twenty-five years ago. Three years previously and again in March, 1928, she had a cough and expectoration and was again in hospital. In May, 1928, she had pneumonia with fever of 102°, cough and rusty sputum. She had bled at intervals since, usually after working in her garden. The sputum began to be offensive in August, 1928. She had a feeling that air did not enter the right upper chest when she breathed. She had lost 20 lbs. in weight. X-rays taken in August at Eurkea, California, showed a density with multiple cavities

involving the right upper lobe. Films in October showed a large cavity; the lobe was dense and more shrunken; the smaller cavities had disappeared. The degree of density varied remarkably from one day to the next. The temperature was usually normal, occasionally reaching 100°F.

Physical examination showed a well-nourished woman. The right upper chest lagged. Physical signs over this area varied from day to day; it was some times dull, sometimes air-containing; the breath-sounds were at times tubular, at times amphoric; at other times there were no cavity signs. The breath-sounds were usually diminished in intensity and accompanied by râles. The right upper intercostal spaces were a little tender to pressure. The rest of the chest was normal. The copious sputum was examined repeatedly, but no tubercle bacilli were ever found. Dr. Ophüls examined 7 specimens for tumor cells; none were found.

Dr. Rehfisch reported X-ray examination of October 22, 1928, as follows:

There is a lobar consolidation involving the right upper lobe with slight displacement of the trachea toward the right. There is a definite area of cavitation in the center of the consolidated parenchyma and some coarse, mottled linear shadows running downward from its lower border toward the lung root. There are a few small calcified foci at the left apex.

Conclusion: Pulmonary consolidation, right upper lobe, with necrosis in the middle of that lobe, most likely tuberculous. A bronchostenotic process due to tumor must be considered.

Dr. Chamberlain made the following report on these films:

There is a dense area at the top of the right lung field which can only be explained on a basis of atelectasis of the right upper lobe. The lobe is shrunken to perhaps a fifth of its normal volume, but the interlobar septum can still be made out both in the lateral and in the anterior projections. There is very little detail to be made out in the atelectatic lobe. One of the earlier films, taken elsewhere, shows a cavity in the affected lobe, but this is not seen in our films.

In the left lung apex there is a little granular density which I consider quite characteristic of old tuberculosis scars.

Conclusion: A complete or almost complete closure of the right upper-lobe bronchus is demonstrated by these findings, and it is hardly likely that the cause of this is anything else except a primary carcinoma of the bronchus. The only other possibility which deserves serious consideration would be an old shrinkage of the right upper lobe, result of tuberculosis of many years' standing. On account of the unlikelihood of tuberculosis or abscess producing this picture, I feel that it is almost surely a carcinoma.

Dr. Lloyd Bryan, who was kind enough to examine these films, as well as films after lipiodol injection taken on November 5, made the following report:

The lipiodol injection demonstrates that there is a rounded irregular shadow at the root of the upper right bronchus which is pressing upon the bronchus, giving a partial stenosis. The films taken at this time show considerably more air in the upper right lobe than in the film taken previously. While primary malignancy cannot be definitely excluded, it seems to me that the whole picture can be explained on the basis of a partial stenosis from pressure of a gland upon the bronchus. There is definite evidence of an old tuberculosis at both apices,

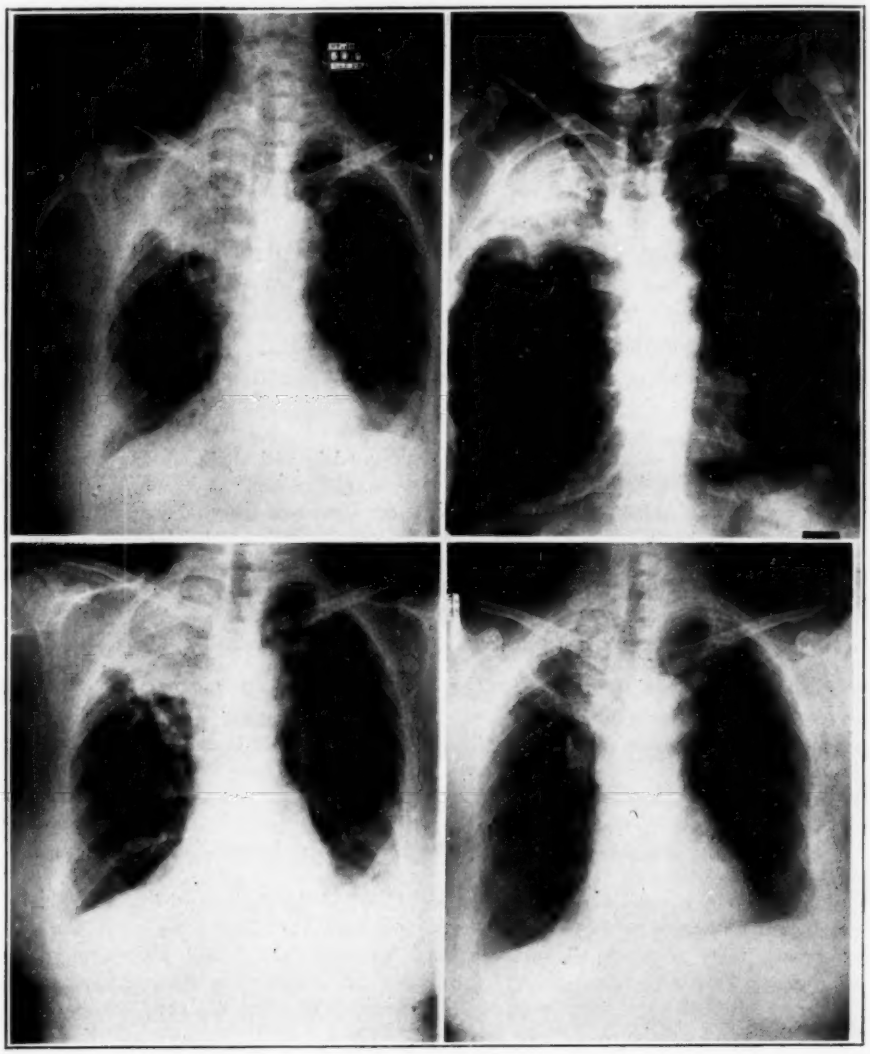


FIG. 29

FIG. 30

FIG. 31

FIG. 32

FIGURES 29–32. Case 9. Intermittent stenosis of right upper lobe.

FIG. 29. October 22, 1928. Moderate density of right upper lobe.

FIG. 30. October 25, 1928. Marked density of right upper lobe.

FIG. 31. October 26, 1928. Partial aeration of right upper lobe. These three films taken in a period of four days demonstrate that the variation in density is due to varying air-content rather than to a tuberculous infiltrate.

FIG. 32. January 8, 1929. Right apex is much clearer; trachea is retracted to right and the right upper lobe is shrunken. The density is therefore due to a varying degree of stenosis rather than to a tuberculous or a cancerous infiltrate.

pleuritis at both bases, and mediastinal pleuritis on the right side. While the presence of tuberculosis does not exclude the possibility of carcinoma, it seems to me that the whole picture can be explained on the basis of an old tuberculosis plus glandular involvement. (Figures 29 to 32).

On October 24, Dr. Harold Fletcher did a bronchoscopy and reported as follows:

The bifurcation of trachea was normal except that the lateral wall of the right main bronchus was much more concave than normal, making the location of the opening of the upper right lobe bronchus difficult to find. To locate the opening of the upper right lobe bronchus, it was necessary to force the patient's head far to the left exerting pressure on the lateral wall of the right main bronchus. The opening was apparently normal in position, but the membrane lining this opening appeared definitely edematous, markedly pale and somewhat glairy. Apparently very little air entered or came out of this upper lobe. The last finding was indefinite. There was a small amount of pus just inside the entrance of the upper right lobe bronchus. No definite obstruction could be seen in it, but the impression given by this examination was that there was an obstruction beyond the opening, probably coming from pressure above the upper right lobe bronchus and pushing somewhat in on the lateral wall of the right main bronchus, above the bifurcation of the upper right lobe bronchus. The last findings also must be put down as an impression rather than an actual proved condition.

It was difficult to decide between intrinsic stenosis; that is, a tumor, and extrinsic stenosis from pressure of a hilar lymph node. It was also difficult to decide whether to explore the chest or to observe the patient further. Finally, however, the prolonged history of recurrent attacks, the presence of old spots at the left apex, the mediastinal thickening below and the definite evidence of basal pleurisy, as well as the concavity which forced the bronchoscopist to turn his instrument to the left before visualizing the right upper bronchus, made the likelihood of enlarged hilar lymph nodes sufficient to lay the question of tumor open to considerable doubt. It was decided to defer operation. The subsequent course has justified the decision, for the patient improved and has remained well for the past five years.

Repeated observation, especially if the apex is now open, now closed, will permit of a diagnosis of stenosis, for fibrosis does not come and go in the interval of a few days or weeks—and tumor stenosis usually, although not always, increases with time rather than recedes.

Case 10

Dr. Philip King Brown was kind enough to refer Miss E. S., *aet.* 48, on August 7, 1932. In 1915 a tuberculous peritonitis was found by laparotomy. The patient had some cough at the time. In 1925 she had a wheezy cold and was treated for asthma. In March, 1931, she consulted Dr. Crosby of Oakland who found tubercle bacilli in the sputum and sent her to Alum Rock Sanatorium. Pneumothorax was induced with some difficulty in November, 1931, and

stopped in March, 1932, on account of adhesions. Pneumothorax succeeded in reducing her sputum from two to one sputum cups a day. Her cough has always been hard and troublesome. She has been hoarse since 1931 and aphonic since April, 1932. She suffers much from "asthmatic" attacks of *inspiratory* dyspnoea. The right upper chest seemed to lag a little. The right apex was dull. Over the right clavicle the breath-sounds were amphoric and high-pitched. There were diffuse wheezing rhonchi and râles everywhere over

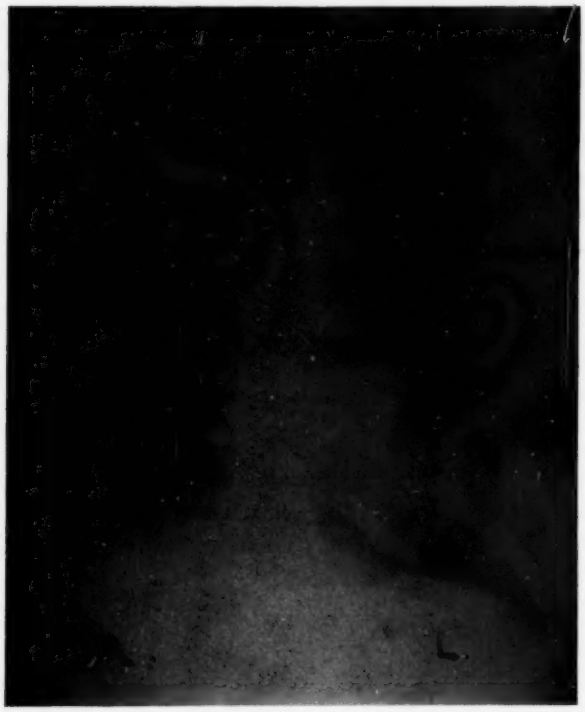


FIG. 33. Case 10. Stenosis right upper lobe. Right apex airless and retracted

both lungs. A painful rectal examination produced a severe attack of purely inspiratory dyspnoea, lasting three to four minutes. Temperature 37°–37.6°C.; pulse 90–100; respiration 20–24. *Sputum:* 2–5 oz. in twenty-four hours; contains tubercle bacilli (figure 33).

Bronchoscopy on August 10, 1932, revealed reddened but not ulcerated vocal chords. The carina was much deformed, having the appearance of a deflected nasal septum. It was beset with yellowish white spots which, after they were removed by suction, bled. The whole wall of the trachea was thick, the cartilages being nowhere clearly visible through the thickened mucosa which was

beset with tiny cheesy white spots. The right major bronchus was deformed and scarry, having a triangular cross-section in some places and a quadrangular one in others. Much secretion came from this side; the lower-lobe bronchus contained secretion, was red, but otherwise normal. The left bronchial tree was not entered; seen from above it was normal. A small cheesy granulation was removed from the trachea for examination (figure 34).

Diagnosis: Tuberculous laryngitis; tuberculous tracheobronchitis (right bronchial tree); sclerosing tuberculous peribronchitis.

The shadow of a stenotic upper lobe may be the ordinary fan-shaped one, but the fan may also be narrow and document itself merely as a moderate widening of the upper mediastinal shadow. Lateral films of this region give no information but oblique ones may. Both upper lobes may be stenotic. In one such patient the outstanding symptom was dyspnoea.

FIG. 34. Case 10. Deformity of right bronchial tree; carina deformed. Right major bronchus partially obstructed. Tuberculous granulation on tracheal wall.

Case 11

Miss B. S.: was seen at Palo Alto on November 12, 1931, with Dr. Russell Lee, to whom I am much indebted, not only for calling me to see her, but for the autopsy. She had complained of fatigue and a slight fever in 1926. Films at this time showed a rounded shadow one-half the size of a pullet's egg at the right hilum (doubtless a lymph node) and increased peribronchial markings on both sides. Films dating from the last four years show a broad upper mediastinal shadow (figure 35). Old films were said to show a bilateral apical pneumothorax! This was probably an apical emphysema. A year or so ago she was seen by Dr. Jones of Los Gatos for dyspnoea. On his first visit Dr. Jones told her that her left lung was closed and later he stated that it had opened. Since this attack Dr. Lee has always heard breath-sounds on both sides of the chest. For the ten days preceding my visit, she had been excessively dyspnoeic and had an inspiratory stridor.

On examination she was cyanotic and fighting for breath. Both supraclavicular fossae were retracted. The larynx moved downward on inspiration

for a distance of 1 to 2 cm. She stated that her chest felt tight directly under the sternum and over the left apex. A broad strip over the upper mediastinum was dull. There were multiple râles all over the right side, especially at the right base anteriorly, but the left side of the chest was silent. Hooking the fingers under the clavicles and pulling up on the thorax with them gave her a sense of relief. She died of increasing dyspnoea on November 16, 1931. Dr. Lee got permission for an autopsy which was done five hours after death.

Autopsy: A catheter was inserted through the nose into the trachea. Barium-gelatine was introduced into the catheter by gravity. It soon ran out of

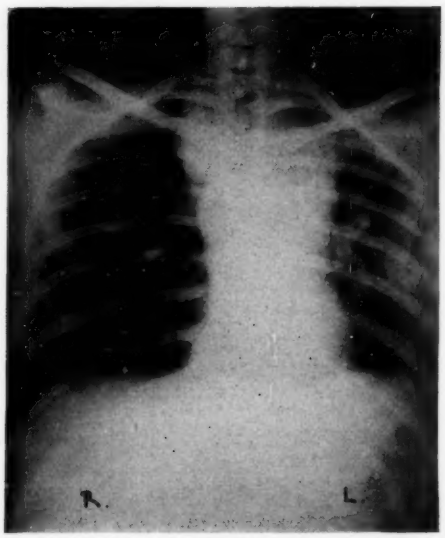


FIG. 35. Case 11. Density of medial portion of upper part of both chests, making the impression of a broad upper mediastinal shadow, but actually due to an atelectasis of both upper lobes following an ulcerative tuberculous stenosis of both upper-lobe bronchi.

the mouth (figure 36). The chest was opened. Under the sternum lay the black and totally atelectatic upper lobes, each to one side of the trachea. Laterally to them lay the emphysematous and much distended lower lobes and right middle lobe pushing the atelectatic lobes to the midline (figure 37). There were enlarged pink lymph nodes to each side of the trachea. It was doubtless the atelectatic lobes, and not the lymph nodes, that had caused the broad mediastinal shadow seen in the X-ray. The specimens were hardened in formaldehyde. When cut open, one saw in the top section the atelectatic upper lobes, the left one of which contained some barium in peripheral ulcerated, bronchiectatic cavities with which it was riddled. The bronchus was

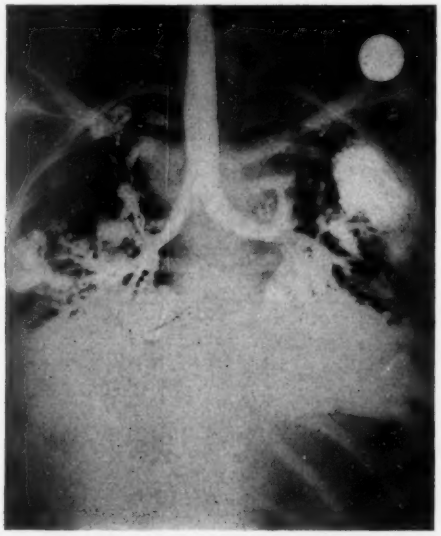


FIG. 36. Case 11. Barium-gelatin has been injected into the trachea postmortem. The lower-lobe bronchi and their branches have filled, but the upper bronchi refuse to fill, and no barium has entered the atelectatic area.

FIG. 37. Case 11. *Lung:* Lower portions much dilated. Both upper lobes are much decreased in size and are completely atelectatic; they are represented by the small dark structures to each side of the mediastinum.

followed toward the midline. It was ulcerated, thick-walled, and its mouth was also ulcerated and irregular where it joined the left major bronchus (figure 38). In the upper part of the left lower lobe was a tuberculous cavity, half the size of an English walnut and filled with green pus. All of the alveoli of the lower lobe were dilated, and scattered about the periphery were fresh, gray tubercles. The bronchi in the lower part of the left lower lobe were probably somewhat wider than normal, but their walls were soft. The bronchus to the right upper lobe was followed with great difficulty. The hardened bar-

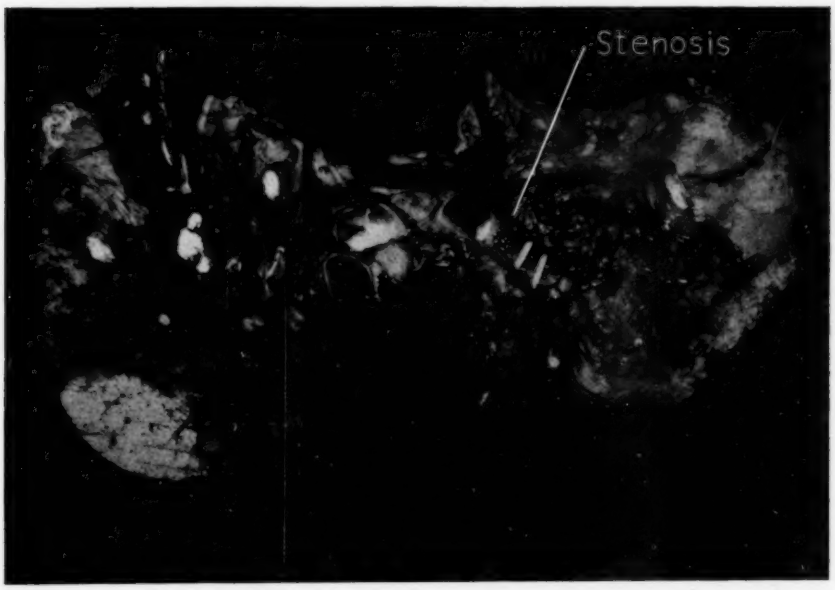


FIG. 38. Case 11. Cross-section of lung at the level of one upper lobe bronchus. The lumen of the bronchus which is sectioned longitudinally is held open by two pieces of matches. Just to the left, at the entrance of the upper-lobe bronchus into the main bronchus, one sees the caseous ulcerated stenosis.

ium-gelatine was removed from the bronchial tree without finding an opening to the upper lobe. There was visible merely a depression which was entirely closed over by a membrane. The bronchus appeared on a section of the lobe. No barium could be made out in it. A probe passed through it came up against the above-named depression, but did not penetrate into the bronchial lumen. There may have been a very fine opening, for at one place it seemed as though a little barium were contained in a peripheral bronchus. This, however, may have been chalk. The right middle and lower lobes also contained a fresh dispersion of tubercles, partly suppurating. The right lower-

lobe bronchi were perhaps a little dilated, but were thin-walled and soft. Large bronchial lymph nodes beset both the trachea and the major bronchi.

Diagnosis: Atelectasis of both upper lobes due to total stenosis of right upper lobe bronchus, and partial stenosis of left upper-lobe bronchus, the latter having fresh tuberculous ulcers on its wall: fresh tuberculous dissemination in both lower lobes and right middle lobe: emphysema of lower lobes.

Stenosis of the right middle lobe: This may give rise to a right-sided parasternal dulness, to diminished breath-sounds and crepitations over this area. The dulness, which adjoins the heart dulness, may be difficult to judge of, and the changes in breath-sounds are often easier to hear after seeing an X-ray film than before. The X-ray shows a lower right-sided shadow of various dimensions and shapes. It may be quite small, triangular (in the anteroposterior projection), with the base upward or downward; or the whole base may be gray. A right lateral projection will serve to place the density in the anterior part of the chest, but it may be difficult, even with the aid of stereoscopic anteroposterior and lateral projections, to distinguish the density from that of an effusion between the right middle and right lower lobes. An aspirating needle may give the desired information and injection of opaque oil (unless contraindicated by a tuberculosis which one fears to reactivate) almost certainly will. For, if, under the screen, the patient leans forward and to the right and one watches the oil flow, one should see it puddle at the bifurcation of the right middle and lower bronchi and refuse to enter the middle one, or slowly trickle through the stenosis.

The bronchoscope gives definite information. The right middle lobe bronchus is not difficult to identify: the stenosis may be seen and entered with the bougie.

Case 12

The accompanying films (figures 39 & 40) show a nontuberculous stenosis of the right middle bronchus, the mouth of which was seen in the bronchoscope to be obstructed by a granuloma. The chronic suppuration probably followed a postoperative embolism.

Stenosis of lower-lobe bronchi: Ulceration rather than shrinkage seems more often to underlie lower-lobe than upper-lobe stenosis. Although of all lobar stenoses lower-lobe stenosis is perhaps the easiest to recognize, the stenotic lower lobe is more often mistaken for fluid than the others. Retraction of the chest-wall, especially of the intercostal spaces

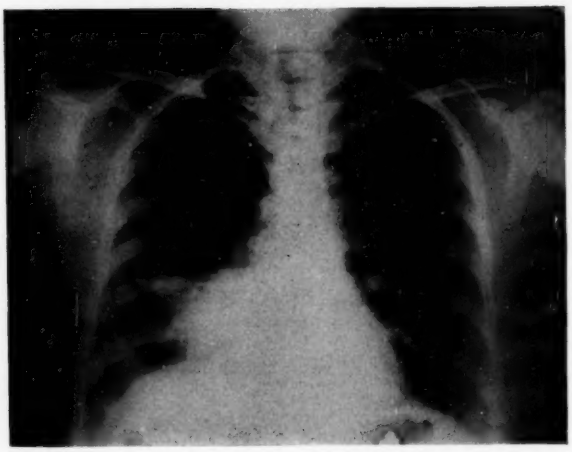


FIG. 39. Case 12. Triangular shadow lower right side of chest, corresponding to atelectatic middle lobe.

FIG. 40. Case 12. Same. Lateral projection

and impairment of mobility, localized to the lower portion of one-half of the chest, with elevation of the diaphragm and deviation of the mediastinum toward the affected side will, as in other stenoses, awaken suspicion.

There may be dulness and perhaps impaired breath-sounds, and perhaps the intercostal spaces over the affected area may be tender to pressure. It may not be simple to exclude an effusion without an X-ray, but the aspirating needle and the X-ray, which shows the deviation mentioned above and fails to show a shifting level, will make the difference definite. As in middle-lobe stenosis, opaque oil, if not contraindicated, or the bronchoscope will both demonstrate absence or presence of a stenosis with certainty.

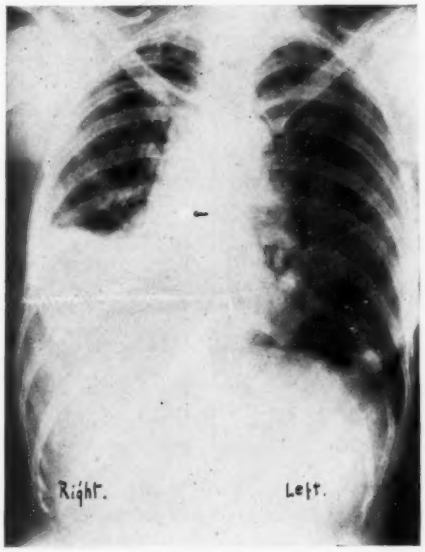


FIG. 41. Case 13. Arrow points to chalky lymph node at right bronchial bifurcation. Marked contraction of right chest with elevation of right diaphragm and complete dextrocardia. Basal density due to atelectasis of right middle or right lower lobe.

Case 13

A stenographer of forty was seen in September, 1928. She had been hoarse, had coughed for three and one-half years, and had a tuberculous fibrosis with cavitation of the right apex. In the X-rays chalky tuberculous lymph nodes were visible at the tracheal bifurcation.

She was hospitalized at the Community Hospital, San Mateo, where Dr. Knorp kindly asked me to see her again on March 27, 1930. She had suffered much from attacks of wheezing and breathlessness. The left side of the chest was hyperresonant, the resonance extending over the midline into the right chest. There were dulness and crepitations over the right hilum. The right

intercostal spaces posteriorly retracted on inspiration. There was a dull area corresponding to the right middle lobe, but this extended so far backward that it sounded as though there might have been fluid in the interlobar fissure. Over this area one heard a distant bronchial whiff. The heart was retracted far to the right (figure 41).

Bronchoscopy on April 4, 1930, disclosed a normal larynx. The left major bronchus was somewhat flattened on its lateral aspect;—otherwise normal. On the right side one looked into a funnel. The bronchial mucosa was red and boggy and the normal rings were not to be seen. About 2 cm. below the bifurcation the funnel narrowed into an annular stricture with a lumen about

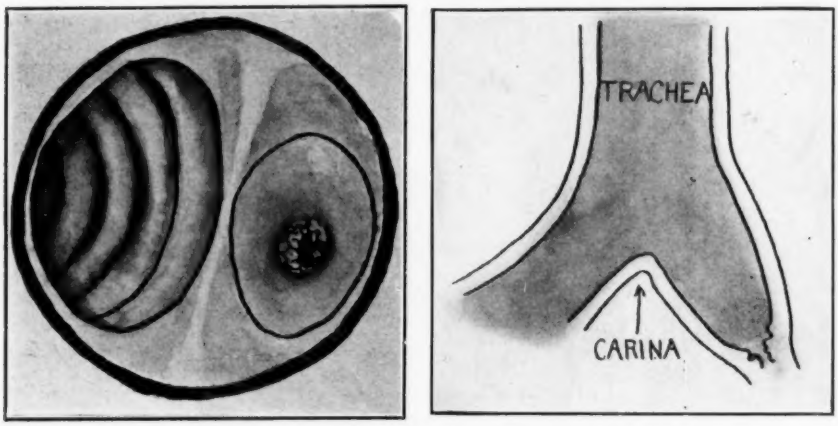


FIG. 42a FIG. 42b

FIG. 42. Case 13. Ulcerative stenosis of lower portion of right main bronchus.
Case 14. Intralobar stenosis of right middle (right lower?) bronchus, with progressive softening, cavitation and finally shrinkage.

4-mm. in calibre. The edges of this stricture, especially on the left and upper aspect, were formed by an ulcer into which chalky white, irregular masses protruded. One could distinctly see the walls widen on inspiration and close on expiration like the mouth of a carp (figure 42).

Diagnosis: Stricture of the right main bronchus below the level of its bifurcation into its middle and lower branches. The mouth of the right upper bronchus, which was not distinctly seen, was probably free and came off at a level above the stricture.

TREATMENT OF STENOSIS OF A SINGLE-LOBE BRONCHUS

Stenosis of a single-lobe bronchus *per se* demands no treatment. Loss of the respiratory parenchyma of a single lobe is negligible. Indeed,

provided there are no toxic secretions retained behind it, stenosis itself may cure a lobar tuberculosis by putting the lobe permanently out of commission. Aseptic unilobar stenosis is probably rarely recognized unless radiographically. It may produce no clinical symptoms. Stenoses, which manifest themselves clinically, which we are at pains to recognize and which we shall consider for treatment, are those which cause retention of pus either in cavities or in distal bronchi. They cause fever, sepsis, cough and continued expectoration. They lead to septic cavitation or bronchiectasis or both. Evidently they must be dealt with otherwise than are the usual forms of tuberculosis; evidently attempts at collapse will make matters worse instead of better, unless by some lucky chance collapse straightens a bronchial kink, or in some other way releases the stricture. Ordinarily, compressing purulent secretions behind a blocked outlet is not a rational way of treating a suppuration; neither is it of treating an infected stenosed lobe.

The rational way would be either to drain the infected focus or to remove it entirely. The proposal may not be so utterly unreasonable. Surely repeated disaster has taught us to approach drainage, or any direct attack upon an intrapulmonary tuberculous suppuration, with great misgiving and reluctance. However, if stenosis can be proved,—preferably by the bronchoscope,—and if by the same means a persistent suppuration can be demonstrated behind the stenosis and the rest of the lung can be shown in all probability to be free, then drainage of a stenotic lobe or its removal may be indicated. Two successful attempts may serve to illustrate:

Cases 14 & 15

14: Tuberculous stenosis of right middle (right lower)? lobe; persistent sepsis from infected cavity. Thoracotomy and drainage: An Italian woman of forty-one, referred by Dr. Ryfkogel and Dr. P. K. Brown, was first seen October 28, 1924. In January, 1924, she began to cough and expectorate a stringy mucus; the sputum became purulent and in June, 1924, tubercle bacilli were found in it. In August, 1924, she entered St. Luke's Hospital with fever and expectoration of several ounces of yellow sputum per day. A wedge-shaped shadow surrounding a central cavity in the centre of the right chest was seen in the X-ray films (figures 43 to 46). Although the expiratory excursion of the right side was but little diminished, this side of the chest was dull, with a tympanitic note toward the axilla and the middle of the chest. The breath-sounds were much diminished and the whole chest was full of squeaks and crepitations. The left side was free. Artificial pneumothorax was attempted in four places

FIG. 43

FIG. 4

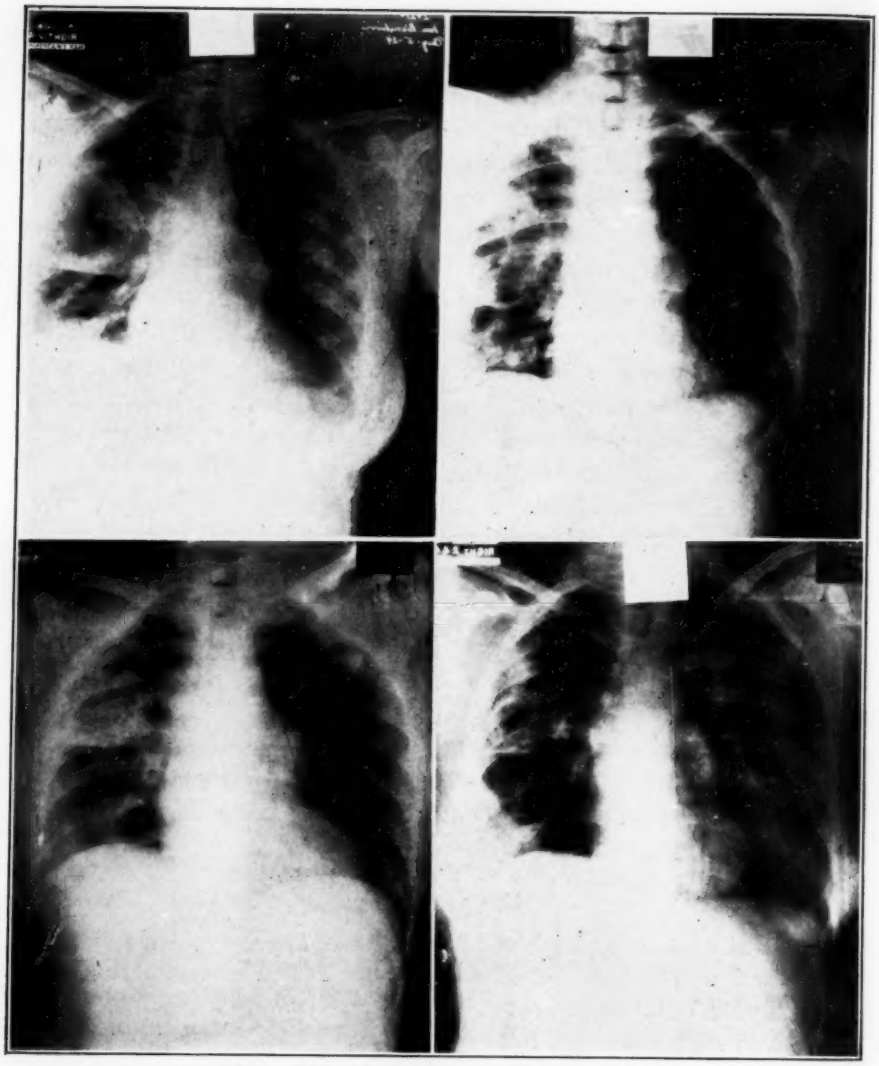


FIG. 45

FIG. 4

FIG. 43. August 5, 1924. Right lower lobe stenosis with cavitation.
FIG. 44. Case 14. August 14, 1924.
FIG. 45. Case. 14. September 2, 1924.
FIG. 46. Case 14. September 17, 1924.

without success. Thoracoplasty was thought inadvisable. She continued to have fever and much expectoration. The phrenic nerve was avulsed August 9, 1925. There was no improvement after operation.

In November, 1926, she reëntered St. Luke's. Bronchoscopy by Dr.

Fletcher revealed a thick, chronically inflamed tracheal and bronchial mucosa. Beginning about one inch below the bifurcation, the right main bronchus was flattened posteriorly, gradually shutting off the tube which ended in a mass of granulations about the mouth of the lower right bronchus. Lipiodol was injected beyond this mass with a cannula. The X-ray taken after this bronchoscopy was reported as follows: The right lung-field distal to the bronchostenosis contains a few small irregular blobs of lipiodol suggesting sacculation of the dilated bronchi.

On January 22, 1927, after more than two years of conservative treatment, it was decided to operate. The notes read:

On account of cavity in the right lung, with persistent sputum in amounts varying from 100 to 200 cc. a day, with bronchial stenosis on the right side, after considerable hesitation, it is decided to open the cavity. This is done because the extreme thickness of the pleura, the fibrosis of the lung, and the central location of the cavity make it seem unlikely that an extrapleural intervention would succeed in collapsing it. Therefore, the 7th, 6th, and 5th ribs are resected.

The pleura is half an inch thick and perhaps over; it is hard as bacon-rind. A needle thrust through it medially withdraws air. This air still comes when the needle is moved over a distance of 1 to 2 cm.; and another needle introduced at a distance of 2 cm. from the first still withdraws air, thus demonstrating that the cavity is a large one. Therefore, with a Percy cautery a funnel-shaped piece of the parietal pleura is resected in several sections, making an entrance of perhaps 1.5 inches across. The point of the cautery suddenly plunges into the cavity, traversing multiple smaller cavities in the lung. The cavity is drained with a rubber tube and packed with iodoform gauze. The wound is left open.

The bronchial stenosis was demonstrated by the fact that no air was expelled from the drainage opening when the patient strained or coughed.

Following this drainage operation the temperature rapidly dropped to normal, the patient gained weight and strength, cough and expectoration ceased, and tubercle bacilli disappeared from the discharge. She was sent home and was able to work hard, cooking and doing the housework for a country hotel, until her death in November, 1930, which occurred instantly following an injection of neoarsphenamine. A coroner's autopsy showed the right lung to have shrunken to the size of a fist. The tuberculosis was completely obsolete. The aorta was syphilitic.

15: Thoracoplasty for tuberculosis of left apex; persistent sputum. Stenosis of left lower lobe. Various compression operations. Finally lobectomy of the left lower lobe: Dr. Philip King Brown kindly asked me to see Mrs. L. K. on February 27, 1926. She had complained of a cough and fatigue in the Spring of 1924. In July, 1924, a massive artificial pneumothorax with displacement of the mediastinum had occasioned much dyspnoea. The pneumothorax, therefore, was allowed to recede, with improvement of the dyspnoea. Pneumothorax was stopped in 1925. In 1927 the upper seven ribs were resected. The

patient continued to expectorate but the sputum was free from tubercle bacilli. Her dyspnoea returned and she was subject to asthmatic attacks, for which she was treated by Dr. Sidney Shipman. The lower left chest was silent and flat; a cavity with a fluid-level was demonstrated in the left lower lobe. Bronchoscopy on January 16, 1932, revealed a normal right bronchial tree, but a blunt carina that deviated from the left, anteriorly, to the right posteriorly.

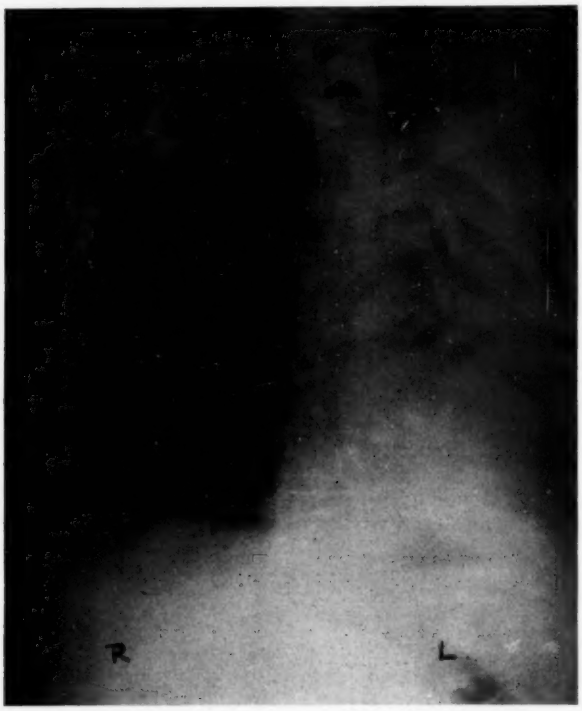


FIG. 47. Case 15. Stenosis of left major bronchus after resection of six upper ribs. Left base airless, heart retracted to left: left diaphragm moderately elevated.

Following the left major bronchus one looked into an irregular, reddened cup-like funnel, which admitted at first the finest bougie, about the size of a knitting needle, then later a no. 12 French bougie (figure 48). After passing the bougie, pus welled up into the opening from the left lower bronchus, the mouth of which was round, but not more than 2 mm. in diameter. After sucking off the pus the bronchial opening was visualized. It was red, but not ulcerated. On January 25, 1932, the 8th and 9th ribs were resected with the idea of draining the cavity in the stenotic lower lobe. However, after the ribs were removed the wound retracted, the patient began to expectorate and the lung retracted

so deeply that it was thought better to await the result of this additional rib resection than immediately to drain, for it was considered that drainage, if necessary, could easily be done later through the flap just outlined.

This resection had no effect on expectoration, so on April 4, 1932, the old scar was reopened and the lower lobe compressed with gauze after the manner of Garré. The sputum persisted, and on October 14, 1932, the left lower lobe was removed. Hereupon expectoration ceased and the patient has had no

FIG. 48. Case 15. a & b. Same patient. Stenosis of left major bronchus following upper partial thoracoplasty.

a. Diagram of bronchial tree showing stenosis of left major bronchus.

b. View at section AA, showing left-sided stenosis and portion of normal right bronchial tree.

cough or expectoration since. Section of the extirpated lobe showed complete atelectasis and the presence of numerous bronchiectatic cavities.

DIFFUSE OBLITERATIVE BRONCHIOLITIS

Finally there remains to discuss an entirely different picture and an entirely different stenotic process, the foundations for which seem not too solid. One not infrequently encounters diffuse tuberculous emphysema. This has been described as tuberculous asthma and adduced to tuberculous allergy and to other causes equally mysterious. The emphysema in

question has been seen in tuberculosis accompanying or implanted upon an old chalicosis—in quartz miners—but also in others. This emphysema is due, I think, to a diffuse stenosing bronchiolitis, comparable to the fibrous bronchiolitis first described by Fränkel (3) in patients subjected to the fumes of destructive gases. The lungs are enormously dilated, so that at autopsy it gives some trouble to deliver them through the ordinary autopsy incision. In case 17 the centre of the lungs was occupied by a chalky mass, which threaded its way to the periphery like a huge mass of coral. The peripheral alveoli were irregularly dilated, some areas more or less uniformly in the form of small emphysema bubbles, about 1 to 1.5 mm. in diameter, others in the form of huge bullae, the size of a hen's egg (*cf.* figure 9). The lungs of one of the patients were injected postmortem with a barium-gelatin mixture. The mixture filled the bronchial tree as far as the bronchi of the 2nd, 3rd and 4th order, but none of the finer bronchi or bronchioli (figure 49). Clinically these diffuse bronchiolar stenoses were characterized by the most intense dyspnoea (not expiratory as in true asthma, but inspiratory) and by an inspiratory stridor. The dyspnoea was not spasmodic but continual, interspersed by suffocative attacks, in which one of the patients died. (Others probably met a similar end, but I could observe only this one.) The chest was not barrel-shaped, but rather flat; the intercostal spaces, however, were wide and the ribs far apart.

Physical Signs: Resonance was increased, the breath-sounds diminished, inspiration prolonged. The chest was full everywhere of squeaks and rhonchi and râles. The patients were ashen-gray rather than cyanotic, the pulse was small and rapid and the blood-pressure low. None of the patients had oedema of the extremities, nor effusion into any of their body cavities. The temperature was but little or not at all elevated. The blood count was normal; one patient was anaemic; none had an increase of haemoglobin or red cells.

The X-rays showed a central density, due in many instances to perihilar infiltration. One patient subjected to exploratory mediastinotomy had enlarged peritracheal lymph nodes, but they were smaller than the X-ray shadow would lead one to suppose, so that but a small part of the hilar shadow may be presumed to have been cast by the lymph nodes but most of it, I suppose, by hilar infiltrates.

Cases 16, 17 & 18

16: Mrs. R. K., a woman of twenty-nine had an uncle and a sister who were asthmatic. After the birth of her second baby she had an illness thought to be

influenza and two months later had her first attack of asthma. These attacks have continued since; they last six weeks and are so severe that she is confined

FIG. 51

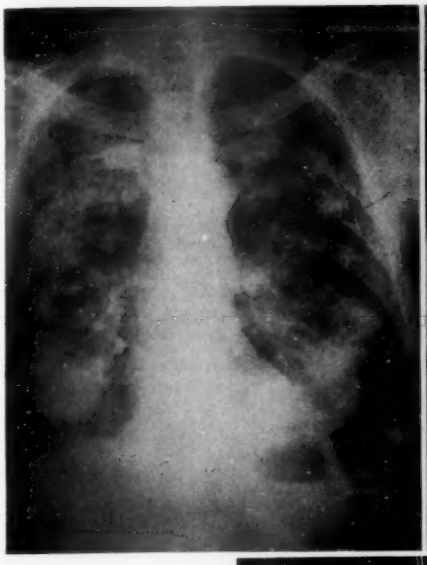
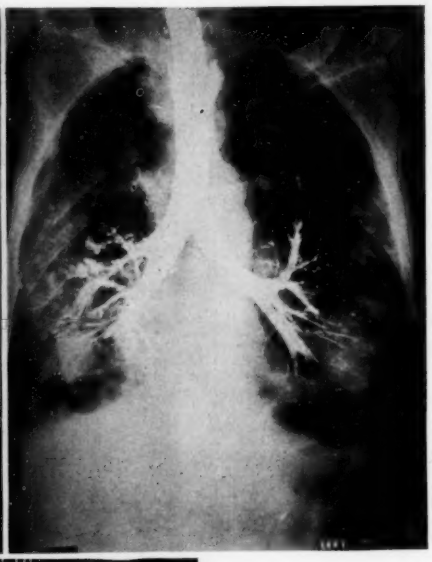


FIG. 49a



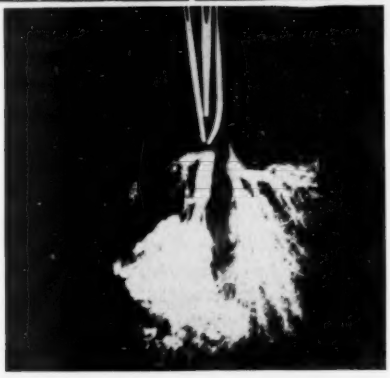


FIG. 49b

FIG. 49. Case 17. a. Obliterative bronchiolitis. Barium-gelatin injected postmortem has filled the larger bronchi, but only a few of the smaller ones and none of the alveoli.

b. Normal lung injected for comparison.

FIG. 51. Case 17. Central chalicotic deposits. Peripheral emphysema most marked at bases. Diffuse stenosis of smaller bronchi.

to bed and has to sleep sitting up. They are accompanied by much coughing and are due to no known cause. They are ushered in by attacks of sneezing. Her temperature is usually normal.

On examination June 30, 1927, the sternal notch and the supraclavicular fossae were retracted on inspiration, but expiration was free. The chest was flat rather than barrel-shaped. Purring and snoring rhonchi were heard everywhere over both lungs. The breath-sounds were much diminished, especially at the base where they were scarcely audible. At about the level of the scapula the breath-sounds began to be normal on both sides. The heart was not enlarged; the sounds were ringing, as though the heart were working under difficulties.

The red-cell count was 4,800,000; haemoglobin 88; the white cells 16,200. After much search tubercle bacilli were demonstrated in the sputum by the antiformin method. Skin tests with a hundred different foreign proteins gave no positive reaction. Dr. Rehfisch made the following X-ray report:

Chest: Fluroscopically both lung fields give the impression of markedly increased translucence. The diaphragm does not move at all on either side and both domes are deformed by puckered pleural adhesions.

The plates show pleural scarring at both apices and between the lobes on the right. There are definite mottled shadows at both tops and the peribronchial markings present an unusually beaded appearance throughout both lung fields. Whether this is entirely a question of artifact due to the increased amount of air in the emphysematous lungs or whether the beaded shadows represent actual foci of consolidative pathology is difficult to say. That such pulmonary pathology exists at the apices at least, however, is extremely probable [figure 50].

Conclusion: Emphysema. Pleural adhesions and thickening. Apical pulmonary tuberculosis with probable acute disseminated tuberculosis of the miliary type.

Dr. Harold Fletcher did a bronchoscopy on August 14, 1927, and reported as follows:

Examination showed a slight suspicion of flattening along the right wall of the trachea. The bifurcation was normal; the right bronchus was somewhat congested and had a very slight tendency to bulge in from the left side about 1 to 1½ inches below the bifurcation. The left main bronchus was almost completely closed about ½ to ¾ inch below the bifurcation. The closure appeared to come from a bulge in the wall from the left and somewhat anteriorly. The remains of the lumen gave the appearance of being flattened out even from the right posteriorly.

This examination checked the preliminary diagnosis of stenosis of the left main bronchus.

At several subsequent examinations the breath-sounds were consistently diminished on the left side. She was discharged to her home in Napa, where she died in a suffocative attack. She was very blue and her doctor said her heart had given out.

17: Mr. B., a man of sixty, had worked as a quartz-miner for twenty years. He quit the mines in 1922 on account of cough. He had coughed for the last six or seven years, perhaps longer, bringing up a grayish and yellowish sputum, streaked with small flecks of blood. He had never had a severe haemorrhage.

On examination in May, 1927, he was thin and exceedingly dyspnoeic, wheezing when he breathed. The right base was dull; breath-sounds were diminished over the right. Coarse dry râles were scattered diffusely over both sides of the chest, with coarse moist râles over the right apex anteriorly. The veins of the upper chest were moderately dilated. The rib cage was rigid, but both sides moved equally. The blood-count was normal. No tubercle bacilli were to be found on repeated examination. The patient denied veneral infection. The Wassermann reaction was once negative, once doubtful.

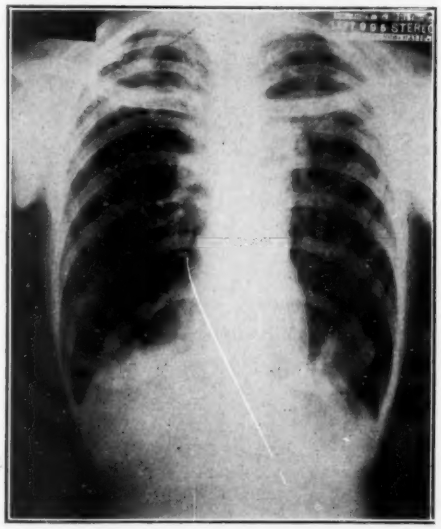


FIG. 50. Case 16. Diffuse tuberculous stenosis of smaller bronchi. Marked dilatation of lungs and rib cage. Note wide chest and narrow waist. Small heart.

Dr. Rehfisch reported the X-ray findings as follows:

Chest: The subclavicular portion of both lung fields is diffusely sown with dense cottony areas of mottling which become more extensive and opaque as one approaches the two bases. The apices are relatively clear. The mediastinal contents are pulled somewhat to the right and the lateral view shows a practically opaque posterior mediastinum. The diaphragmatic outline is most irregular on both sides, due apparently to extensive pleural diaphragmatic adhesions [figure 51].

Fluoroscopically the diaphragms show practically no motion on either side.

Conclusion: Advanced pneumoconiosis.

Autopsy: The patient died during a suffocative attack. Autopsy revealed enormously dilated lungs, the left one reaching into the right chest to the right sternal border and overlying the heart. The diaphragm lay at the level of the sixth rib.

There were perhaps two ounces of clear yellowish fluid in the heart sac. The heart was a little larger than the fist; it contained large quantities of still-liquid dark blood. The right ventricle was somewhat dilated and its wall thickened to perhaps 3/8 inch. There were some slight patches of atheroma around the mouth of one coronary, but the aorta and coronaries were remarkably soft for a man of his years.

Both lungs were attached to the chest-wall by numerous bands of firm adhesions, but the pleural cavities were by no means obliterated; there was no free fluid in them. The lungs were so greatly dilated that they could be with difficulty extracted from the chest and it is noteworthy that they did not collapse when the chest was opened. In both lungs, especially the left, were numberless bubbles of emphysema, one of them the size of the palm of the hand and occupying the apex of the left upper lobe; there were numerous others the size of a small pullet's egg, making both lower lobes appear knobby and lobular. The walls of these sacs were thin as paper.

In the centre of both lungs one could feel a mass of chalky hardness threading its way through the parenchyma, evidently following the bronchi. In the right lung the surface section of this central hardness was about the size of a dollar (*cf.* figures 9a & b).

The lungs were purple and much congested, as were all of the inner viscera,—both thoracic and abdominal. Along the hilum and trachea lay packets of firm black lymph nodes, the largest the size of a walnut. These did not appear at any place to constrict the tracheal or bronchial lumen and I think that the constriction lay at the level of the bronchi of the second order or lower.

The liver lay four fingers below the ribs in the right axillary line; it was mottled and congested. The spleen was small, fibrous and firm. The other viscera were markedly congested, but otherwise normal.

Barium injected into the cadaveric trachea filled the bronchi of the first and second order and then stopped; the finer bronchi and bronchioli were not injected (*cf.* figure 49).

18: A power-lineman of 39 had what was called influenza, without cough but with fever, in 1921; he recovered perfectly from this. In 1922 he had a second attack, also without cough. In January, 1929, he had pneumonia and a fever to 102–3°. He was so short of breath that his wheezing could be heard all over the house. He had not much cough or sputum. On examination in September, 1929, I found a thin, pale man with clubbed little fingers. He had an inspiratory stridor; there was no dulness and no râles. X-ray showed a large globular mass in the upper posterior mediastinum, pushing the trachea toward the front (figures 52 & 53). Exploratory mediastinotomy revealed a chain of greatly enlarged and adherent peritracheal lymph nodes, the largest

twice the size of an English walnut. This lymph node was removed. Sections showed old scarred tubercles.

But one of these three patients was bronchoscoped. She had a deformity of the left major bronchus. How great a rôle this deformity played is questionable, for both sides of the chest were equally affected, clinically and radiographically.

The patients were permanently bedridden, or should have been so, for they were incapable of the slightest exertion without alarming dyspnoea.

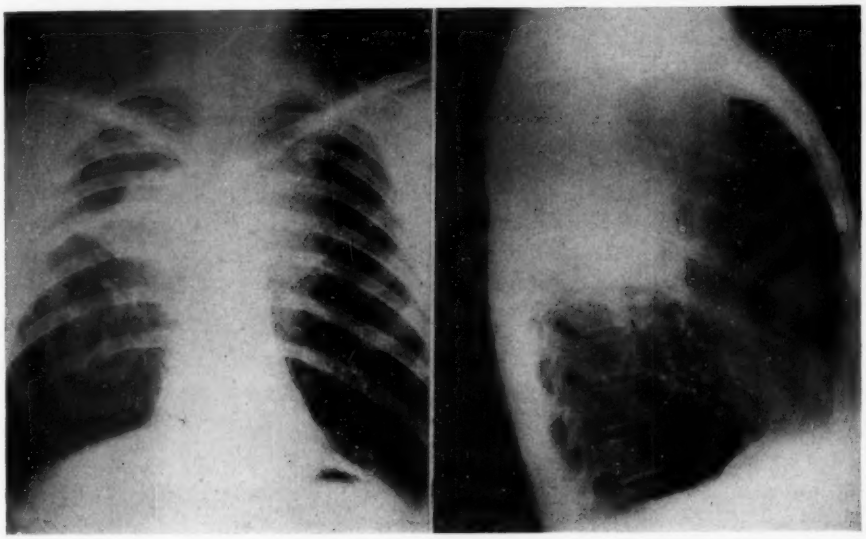


FIG. 52 FIG. 53

FIG. 52. Case 18. Large hilar shadow and perihilar infiltrate with peripheral emphysema.

FIG. 53. Case 18. Same patient. Lateral view localizes a mass in the posterior mediastinum.

They were somewhat helped by ephedrin. How else to have treated them I do not know.

SUMMARY

Stenosis of the air-passages from the trachea to the bronchioli is not infrequently due to various tuberculous processes.

These processes, their anatomy and their effects are described; the clinical picture of stenosis at various levels and various sites is dis-

cussed. The signs, clinical, radiographic and bronchoscopic, are presented and an attempt is made to explain them. Treatment is briefly discussed and it is hoped that the attention of those interested in tuberculosis may be drawn to these frequent, therapeutically important, but rarely diagnosed, lesions.

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ARTIFICIAL PNEUMOTHORAX IN THE TUBERCULOUS DIABETIC[1]

J. J. WIENER AND JULIUS KAVEE

Therapeutic pneumothorax as a form of treatment in the tuberculous diabetic has been the subject of passing comment by many authors. We have however been unable to find a report of a large series of cases so treated and studied. This prompted us to undertake the following analysis. Twenty-six cases of active pulmonary tuberculosis complicated by diabetes mellitus were treated in the wards of Montefiore Hospital with artificial pneumothorax. Of this number nineteen have been induced since January, 1930, when special interest was aroused in this problem. The group chosen for collapse therapy was selected from among more than two hundred cases in which the two diseases coexisted. It is noteworthy that the general mortality of the tuberculous diabetic on hospital service closely approximated that of the group reported by Fitz in 1930. In his group 68 per cent were dead one year after the diagnosis of both diseases had been made; in our series the percentage was 59 and most of the rest were sliding downward. The cases chosen for treatment had active pulmonary tuberculosis with tendencies to progression; and, with a single exception, were febrile. It should be mentioned that in the afebrile case the lung was collapsed with the view of stopping a pulmonary haemorrhage. The diabetes could be considered mild in six of the cases, moderately severe in sixteen, and severe in four. Ketosis was not infrequent at the time of admission in the latter two groups. However, the metàbolic disturbances were fairly well controlled and, as there were no diabetic deaths, no relationship to the ultimate prognosis could be traced to the course of the glycosuria. This will therefore not be the subject of further reference.

The age incidence of our patients closely approximated that observed in diabetics in the general population. Nineteen were over forty years of age; only five were under twenty-five; the youngest of these was eighteen; and four were between twenty-six and forty years. It is very

[1] From the Tuberculosis Division of the Montefiore Hospital and Country Sanatorium, Dr. Maurice Fishberg, Chief of Service.

interesting to note that the age of the patient has had no effect on the ease of induction of the pneumothorax, the extent of collapse obtained, or the ultimate benefit derived. In fact, in one of our patients who was seventy years of age an excellent result was achieved.

Of our patients eighteen were men and eight women. The difference between the number of men and women was at first attributed to the fact that twice as many beds at Montefiore Hospital were occupied by men as by women. However, of the nine patients under forty years of age only one was a female, whereas eight were males. In the group above forty years the number of females was seven. This would tend to indicate a greater tendency for the young adult male diabetic to acquire pulmonary tuberculosis. In the older group the numbers of males and females which came to our attention were about equal.

In nineteen the left and in ten the right lung was collapsed. This number includes one in whom a bilateral pneumothorax was induced. This is in accord with the fact that in nondiabetic patients the left lung is more often in need of therapeutic collapse than the right. Two of the cases had the disease strictly limited to one lung. Both of these were bronchopneumonic lesions, and both were limited to the left lung. Ten cases showed bilateral disease, but only one side was apparently the site of the active focus. Fourteen cases had bilaterally active tuberculosis. Ten of these were induced on the left and four on the right because the process on the left was more extensive.

In all our patients tubercle bacilli were found in the sputum on frequent occasions, and practically all presented some evidence of cavitation either on admission or during the course of the disease before pneumothorax was induced. At the time of induction only one of the patients presented symptoms or signs of an extrapulmonary tuberculous lesion.

The lesions were in the main those which have been described as the "diabetic type" best elicited with the aid of roentgenography. The salient features of this type may be described as a soft exudative process spreading from the region of the hilum toward the periphery, most commonly in the midzone of the lung, leaving the apex and at times the extreme base free from disease. When first discovered one may see bronchopneumonic consolidation occupying part of a lobe, the contiguous parts of two lobes, or the entire lung. Very rapidly caseation and liquefaction occur and thin-walled cavities appear. However, on carefully watching the development of the process in the contralateral lung by serial roentgenograms a truer view of the initial appearance of the disease

may be obtained. Then one sees a few scattered acinonodular foci which rapidly enlarge and form various-sized conglomerate areas fusing into the bronchopneumonic zone previously described, and these areas then proceed to multiple cavities of various sizes. This process, however, is reversible, and at times the exudate is apparently absorbed; the small acinonodular areas reappear and are finally replaced by fine string-like shadows indicative of fibrosis. These lines on the film may become so fine that the lungs assume an almost normal appearance on the films. The exudative nature of this process, and the rapidly changing tempo of progression and involution of the lesion, are the outstanding characteristics of this type of tuberculous infection. Exudative is used herein in a clinical sense, backed up by roentgen appearance and not necessarily as a true expression of the pathological findings revealed microscopically.

In all cases the temperature ranged from 101° to 103°F., and all had the symptoms pathognomonic of active pulmonary tuberculosis. In addition to the symptoms of activity either larger or smaller haemoptyses occurred. In only one case was haemostasis the only reason for induction. In another, the immediate reason for pneumothorax was the desire to control severe haemorrhage but here also the dynamic course of the lesion warranted the treatment.

In all 26 cases marked immediate improvement was noted in nine, slight symptomatic improvement in five, and no improvement was observed in twelve cases in three of which a free pleural space could not be found. All nine of the cases which showed marked immediate improvement are still alive and in excellent condition. Of these, six had bilateral lesions. They have been well for periods varying from twenty months to nine years. In 5 cases only slight symptomatic improvement was noted soon after the initial induction; four of these died within a period of five to nineteen months and one cannot be traced since he left the hospital. He was in poor condition at the time of discharge. Twelve cases showed no improvement in the beginning, and eleven of these died within one and twenty months after the induction. The last of this group did not improve at first, but subsequently, after the appearance of a massive effusion collapsing the lung quite completely, the course became afebrile and the disease quiescent.

The common experience, that the best results in pneumothorax therapy are obtained in patients with predominantly unilateral lesions, is also encountered in the tuberculous diabetic. Of the 13 cases that fell into the group in which the lesion was in the main unilateral, ten showed

immediate improvement after the induction of the pneumothorax and seven of these are still well, eighteen months after the initial induction. Of the other three who showed improvement one cannot be traced; one developed progressive disease, miliary tuberculosis and meningitis, dying within two months; and the third, after showing progressive improvement, had frequent pulmonary haemorrhages and died in nine months. Of the 3 cases which did not improve, in one the lung could not be satisfactorily collapsed and he developed a rapidly progressive contralateral lesion; the second had an extensive bronchopneumonic lesion which we were able to collapse only partially. The disease progressed and the patient died five months after the induction. The third showed no immediate improvement, but has since become afebrile and is doing fairly well since the appearance of a massive effusion which produced an excellent collapse of his lung, that had resisted the intrapleural pressure of the pneumothorax.

Twelve cases of this series had bilaterally active disease at the time of induction. Four of these improved immediately. In one case collapse of the left lung resulted in an amelioration of the constitutional symptoms with a reabsorption and fibrosis of the lesion in the right lung. This man is in excellent health at the present time but suffers from peripheral neuritis, associated with his diabetes. In another only partial collapse could be obtained and the pneumothorax was discontinued one month after its inception, but the patient has continued subfebrile though the disease has progressed slowly. The third became afebrile and felt better following pneumothorax, but left the hospital, abandoned the pneumothorax, and died nineteen months after induction. The fourth showed slight improvement, but developed spontaneous pneumothorax and died of the resulting pyothorax five months after induction. Of the 8 cases which showed no improvement, seven are dead. Of these seven, five died of progressive extensive pulmonary tuberculosis, one of miliary tuberculosis and meningitis, and the other of terminal haemoptysis. The average duration of life of these seven was six months after induction. The one alive is desperately ill. These figures reëmphasize the desperate outlook of the patient with active pulmonary tuberculosis in both lungs, the diabetic as well as the nondiabetic. Therapeutic pneumothorax, as a last resort, is as powerless here as in the nondiabetic.

The extent of collapse obtained and the time during which a satisfactory induction was possible had an important bearing on the ultimate outlook. In 3 cases a good start could not be made because no free

pleural space could be found. Two of these are dead and one is hopeless. In 13 cases the pneumothorax refills had to be discontinued within a period of six months, because of massive effusions, obliterative pleuritis or acute fulminating disease. Ten of these are dead, one cannot be traced, one is in fair condition and the other is well.

Four cases received collapse therapy for a period of six months to one year. Of these two died, one is alive and able to work without further inductions, and the other is well, the therapy being continued.

In 6 cases the refills were continued for more than one year. They are all doing well in spite of the initial active and extensive disease. It is quite obvious therefore that in this group a satisfactory pneumothorax maintained for over a year gives the best chance of a gratifying ultimate result.

Improvement was often dramatic, with cessation of haemorrhage, decline of temperature, diminution of cough and quantity of sputum, etc. The patient felt better, the appetite improved and a gain of weight started shortly after the induction of the pneumothorax. However, in only two instances did the sputum cease to be positive for tubercle bacilli. In one patient rapid resorption of the contralateral diseased lung was observed. In 3 cases it seemed as if there was a small decrease in the amount of insulin required to maintain adequate nutrition and minimal glycosuria after an adequate collapse resulted in an amelioration of the febrile and toxic manifestations of the tuberculous process. However, it was frequently easier to maintain better nutrition although the insulin required was not reduced in amount, most probably because the anorexia decreased and the appetite increased following the induction of the pneumothorax.

The usual complications which occur following collapse therapy were observed just as frequently as in the nondiabetic with tuberculosis. In 46 per cent, a complicating pleural effusion was noted. In one case a spontaneous pneumothorax occurred and he died soon afterward. Obliterative pleuritis necessitating the abandonment of the therapy occurred in 30 per cent. Evidently these complications occur as frequently as in the nondiabetic.

From a study of large groups of cases of pulmonary tuberculosis treated with therapeutic pneumothorax, it can be stated that approximately 50 per cent show some immediate amelioration of the toxic symptoms, and that about 25 per cent may become rated as "clinically well." In our small group, fourteen, or 53 per cent, showed marked or slight im-

provement clinically, and ten, or 39 per cent, are well or in fairly good condition one year after induction. This compares rather favorably with the results obtained in the nondiabetic, who are usually of a much younger age-group.

SUMMARY

Twenty-six tuberculous patients with diabetes were given therapeutic pneumothorax. These individuals were on the average older than those commonly submitted to pneumothorax therapy. The tuberculous process was active and progressive. The diabetes did not affect the results obtained, which are no different than among tuberculous individuals without diabetes. The best results were obtained when the disease was predominantly unilateral and when a satisfactory collapse of the diseased lung could be achieved and maintained for more than six months. Age did not affect the type of collapse or the benefit derived. When benefit was derived it occurred soon after the initial induction of the pneumothorax, and the improvement was rather marked and usually continued. Poor results occurred when the disease was extensive and bilateral, and collapse was only slight. Those who were not benefited immediately were only rarely benefited later. The complications encountered in the diabetic were no more frequent than in the nondiabetic.

CONCLUSION

Pneumothorax therapy in the treatment of the tuberculous diabetic gives approximately the same results as it does in cases of uncomplicated tuberculosis. Therefore, in view of the short life expectancy when both diseases coexist and the tuberculosis is active, pneumothorax therapy in the tuberculous diabetic is highly desirable and should be performed early.

SURGERY IN THE TUBERCULOSIS SANATORIUM

LINCOLN FISHER AND BENJAMIN L. BROCK[1]

Alexander has recently written, "The able thoracic surgeon of the near future will, I believe, be both surgeon and internist, and he will, therefore, have a broad concept of the diagnostic and therapeutic problems of the thoracic diseases with which he deals." This is particularly true of the present-day needs in tuberculosis sanatoria throughout the country. It might almost be stated further, that the paradoxical possessor of this desirable combination of interests will, in all probability, have been tempered by suffering personally from this chronic disease which he combats in others. For, just as deeper insight is thus acquired by the internist devoting himself to tuberculosis therapy after personal victory over the disease, how signally poignant becomes the respect of the surgically-trained phthisiotherapeutist for the intricate problems inherent in his new and growing specialty! Intimate contact with thoracic disease in the sanatorium will have sharpened his diagnostic acumen, and, by the same token, a bent for surgery, temporarily interrupted by his own illness, will have been insidiously whetted to full appreciation of the new opportunity for fulfilment of his ambition. Few established general surgeons of our competitive generation can afford the time required fully to familiarize themselves with the basic principles of so recently full-fledged a specialty.

Thus is opened to those fitted for such a task by inclination and by basic training a surprisingly diversified field in internal medicine and surgery. A requisite knowledge of the dual exactions is essential, of course, and no one lacking in either fundamental is ideally equipped. In the realm of collapse therapy it would be difficult to estimate where the internist leaves off and where the thoracic surgeon assumes major responsibility. The two rôles cannot be entirely divorced with due safety to the patient. An intimate knowledge of the underlying pathological processes is essential here, as it must ever be throughout the realm of surgery. This is, however, exceptionally true under the handicap of

[1] Waverley Hills Sanatorium, Waverley Hills, Kentucky.

progressive depletion of the patient, which accompanies protracted chronic disease. Not only is the proposed degree of surgical collapse dependent upon an accurate estimate of the individual patient's general resistance and local reserve, but also, ready modification of tentative preoperative decisions must be anticipated during the course of surgical measures. To make such adaptability possible, the operator's thorough knowledge of intrathoracic mechanics and pathology is required.

Leslie has recently reported the employment of some form of collapse therapy in 77 per cent of a series of 420 patients admitted to the Michigan State Sanatorium. Granting that this figure is even to be approximated in other sanatoria, one can readily appreciate the need for full-time resident surgeons, or else, as proposed by Alexander, close affiliation with a central general hospital used as a "clearing house" for surrounding tuberculosis sanatoria thus enabled to refer their patients to a consulting thoracic surgeon who attends their staff conferences as surgical advisor. The chief objection to the latter arrangement is the necessity for sending patients some distance away from the sanatorium, and the consequent loss of intimate contact with a medical and nursing staff familiar with their previous course and their limitations. No matter how interested or competent the visiting surgeon may be, he is handicapped by lack of complete familiarity with the individual patient's disease. This knowledge is best gained first-hand in the sanatorium. Neither is the general hospital equipped to hold patients for an extended period of observation or convalescence, nor can patients generally afford the financial burden thus entailed. It is profitable to consider further this unavoidable problem from the point of view of economics. In a community such as our own where the sanatorium is financed entirely by public funds of the city and county, a very high percentage of all patients admitted are practically indigent, ultimately if not immediately, so that it is a tremendous advantage to have a fully equipped surgical department in the sanatorium itself. This, as can readily be seen, is a direct saving, since these patients almost invariably would have to be transferred to the free wards of the City Hospital which is already overcrowded and taxed to the limit of its capacity. Relatively few sanatoria are so fortunately situated as regards surgical facilities as is the Michigan State Sanatorium in relation to Alexander's medicosurgical clinic.

The only alternative is evident; namely, the maintenance by each sizeable sanatorium of a resident thoracic surgeon whose special training in phthisiotherapy can be relied upon to aid in careful selection of suitable

cases for surgical collapse. This places the full burden where it properly belongs, upon the shoulders of the sanatorium staff, who are enabled to follow the postoperative course closely, and with added benefit to both the patient and themselves. Only thus is the greatest progress to be made in surgical collapse therapy, and the best results obtained. The patient, in turn, is disturbed no more than necessary, and mental and physical fatigue are reduced to a minimum. At best, many cases are hazardous problems and must be treated with great flexibility of judgment. No hard and fast rules can be laid down before operation, and hence no recommendation is absolute, or unencumbered by the possibility of subsequent modification. It is indeed unfair to shift the burden of such decisions to the shoulders of an already busy consultant, however unselfish he may be with his services. No one can infallibly foretell, for example, whether the limit of safety in any given thoracoplasty will be reached after resection of six, or of two, ribs at that particular stage. This can finally be determined only during actual operation.

At Waverley Hills Sanatorium we have for the past year, covering June, 1932 to June, 1933, done all our major thoracic surgery at the sanatorium, a newly equipped surgical unit having been completed to carry out that project. Even before that time, the minor procedures had been carried out at the sanatorium for some eighteen months, prior to which all surgical cases were sent to general hospitals in Louisville, ten miles distant. The latter course worked hardship on the various hospitals in the case of indigent patients. Likewise, all major collapse cases lost valuable contact with the sanatorium for variable periods of postoperative convalescence. Preoperative observation by the surgeon had rarely been possible. Coördination between the already overburdened surgeon and the sanatorium staff was necessarily curtailed, disadvantageously to both. It became obvious that our percentage of favorable results suffered for want of closer contact and of better facilities for special care.

The new surgical unit was placed under the direction of a member of the sanatorium staff experienced in the treatment of pulmonary tuberculosis, who had had special training in thoracic surgery as well. As operating-room supervisor a graduate nurse was secured who had had good previous surgical experience. In the beginning a nurse anaesthetist was sought to take charge of the operating room, but no such person with requisite surgical training seemed to be available. Very fortunately, a physician of many years' general experience in anaesthesia was found, who

welcomed the opportunity to work with us on our chest cases at a modest fee for each anaesthetic administered. An ex-member of the sanatorium staff, then going into general practice, was glad to stay on half-time as surgical assistant. In addition to the supervisor, one graduate nurse was employed full-time, and other graduates were taken in rotation from our postgraduate classes in tuberculosis nursing at the sanatorium. This personnel has proved adequate and eminently satisfactory. A number of these nurses, interested enough to take postgraduate work in tuberculosis, have shown special aptitude and interest in the surgical phase. Their enthusiasm should prove valuable in the community as a stimulus to early diagnosis and timely surgical intervention.

During the past year, about the same number of thoracoplasties has been done in the sanatorium as had in the previous three years been done for us at a general hospital. The first thoracoplasty completed at the sanatorium permitted discharge of this patient as "arrested" eleven months later, a five-centimetre cavity closed, and entirely sputum-free since the first postoperative month, in spite of a prior Gaffky-X which had persisted for nearly two years. The others bid fair to equal this satisfactory record in their turn. A comparison of the results in these two groups, of about a dozen cases each, already convinces us that our patients have fared decidedly better when operated upon at the sanatorium and kept uninterruptedly under the specially supervised regimen of the sanatorium staff. This is no reflection upon the general hospital, which is so often handicapped by unfamiliarity with tuberculosis and its detailed management. In addition, the sanatorium staff has had a better opportunity to study these patients from a surgical point of view, and this has offered a salutary slant on selection of surgical risks, which could not otherwise have been obtained. This direct responsibility can no longer be shifted or minimized. Furthermore, surgical collapse has been resorted to earlier than heretofore, and the psychological reaction of patients and their families has been noticeably brighter in outlook.

The resident surgeon also interprets the routine X-ray films, giving him splendid opportunity to detect and work up surgical prospects at the earliest indication. A weekly staff conference is held, at which all X-ray films for the previous week are reviewed with primary consideration for the possibility of surgical intervention. In this way, also, postoperative results are more profitably evaluated by the entire staff, as periodical reconsideration of each case is thus assured, from both the X-ray and

the clinical aspect. These staff meetings are informal, and definitely helpful, allowing full vent to every opinion without reservation.

Supplementing thoracoplasty in the armamentarium of surgical collapse, we have utilized extrapleural pneumolysis with paraffin filling ten times in cases which were judged unsuitable for the more serious operation. In seven of these, cavities have been entirely closed, and several have already been discharged from the sanatorium as fully arrested. Two patients have had bilateral posterior extrapleural pneumolysis, and one of these stood very well a supplementary anterior paraffin filling to complete closure of the large cavity on that side. The operating room has been equipped for dark-room surgery, and intrapleural pneumolysis, according to the Jacobaeus-Unverricht method, has been employed with gratifying results in something over 20 per cent of our approximately 150 artificial-pneumothorax cases maintained since this adjuvant measure became available. Of nearly 500 phrenic-nerve operations, the latter half were done in the sanatorium. It is a distinct advantage to have this procedure readily available as an emergency measure for patients with persistent, alarming haemoptysis, when artificial pneumothorax has proved ineffective or impossible because of pleural adhesions. In addition, well over 100 scaleniotomies have been done along with, or supplementary to, phrenicectomy. This measure has proved a valuable adjunct in many cases with apical cavitation. In one-third of these cases scaleniotomy was employed as a late supplementary procedure, six months to three years after phrenicectomy. Closure of a fair number of sizeable cavities afforded proof of the usefulness of this minor operation as a supplementary adjunct in cases in which major surgical collapse was contraindicated or perhaps considered too radical. An attempt is being made to recognize the true indications for the particular procedure employed in each case, and we feel confident that we are arriving at more definite criteria, as time goes on and more accurate conclusions can be drawn. We can wholeheartedly agree with Alexander that

> The optimum time for using the best operation for the particular patient is often of brief duration. The temptation is often great to wait indefinitely for some minor procedure or an incomplete and inadequate pneumothorax, that already has brought about some measure of improvement, to effect a complete cure. In delaying beyond the time when it is likely that that operation has produced its maximum benefit, changes in the lesions or general condition of the patients may occur to contra-indicate further surgical measures that would probably have been effective in bringing about complete healing.

There is little doubt that the surgical era in tuberculosis therapy is profoundly revamping the rôle of the sanatorium into one of more dynamic usefulness. Along the lines of our own present program, it appears probable that there always will be an adequate number of qualified young surgeons, who develop tuberculosis, to supply the majority of sanatoria large enough to be equipped with surgical units of their own. It is already obvious that the average length of necessary hospitalization in sanatoria is being decisively shortened by such timely surgical intervention. Waiting-lists are being cut down to a minimum by this more rapid turn-over and earlier, more effective, sanatorium education is afforded. Patients are removed from contacts in the home shortly after diagnosis is made; when collapse therapy has rendered them bacillus-free they may often continue the "cure" at home with perfect safety to young children and adolescent contacts. Patients are being restored to economic independence with a minimum of hardship to their families. The ensuing five years should bring about even more revolutionary advances, as earlier collapse measures in more suitable cases are instituted with greater frequency, resulting in increasingly swifter and surer arrest of disease. This goal is best attainable, by and large, in the surgically equipped, and collapse-conscious, sanatorium.

We wish to express to Dr. Lawrason Brown our sincere appreciation for his helpful suggestions in preparing this paper.

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LATENT PULMONARY TUBERCULOUS INFECTIONS IN CHINESE ADULTS OF THE PROFESSIONAL CLASSES[1]

G. A. M. HALL AND C. P. CHANG

The work of the Henry Phipps Institute in Philadelphia has done much to emphasize the frequent occurrence of important, potentially active and progressive tuberculous infiltrations in the lungs of apparently healthy children and adolescents, who have been exposed to repeated infections with the tubercle bacillus in the home or school. Such lesions can be demonstrated only in roentgenograms of the lungs, and produce no symptoms or physical signs. Since the year 1922 the routine physical examination by the College Health Service of the Peiping Union Medical College of all persons joining the staff, and all undergraduate and graduate students entering the medical and nursing schools of the College, has included stereoscopic X-ray films of the lungs. A wealth of material has been accumulated which gives valuable information about the frequency of the various types of latent tuberculous disease in the thoracic cavity of young, apparently healthy Chinese of the professional classes. This report is based on the examination of the X-ray films of 1,007 such individuals.

MATERIAL

Only individuals of the Chinese and Korean races, and Eurasians, are included. The vast majority were born in China, and have never left the country. There has been no selection of cases beyond the availability of the desired information in the record of the individual and the exclusion of any individual who had suffered from symptoms ascribable to tuberculosis prior to the taking of the first X-ray films.

For the purpose of classification and of estimation of the effect of exposure to tuberculosis, in the case of nurses and doctors, individuals have been assigned to one of the following six categories, according to their status at the time of the original X-ray studies:

[1] From the Department of Medicine and the Department of Radiology, Peiping Union Medical College, Peiping, China.

1: Medical Students: Recent graduates of both sexes from Colleges and Universities. All had completed a three-year premedical course, and many had received a bachelor's degree in the natural sciences.
2: Nursing Students: Women only, with previous high-school or college education.
3: Physicians: This category includes (a) recently graduated physicians from other medical schools in China (more rarely in Europe or America) entering the hospital as internes; (b) members of the clinical, research, or teaching staff, generally graduates of some years' standing of medical schools in Europe or America; (c) postgraduate students who are qualified physicians, usually graduates of other medical schools in China.
4: Nurses: Graduate nurses who have been trained in other hospitals in China, or in a few cases abroad.
5: Nonprofessional Staff: Secretaries, dietitians, pharmacists, etc.
6: Graduate students other than physicians.

The age distribution of the individuals included was as follows:

	Number	*Per cent*
Less than 20 years	30	2.9
20 to 29 years	857	85.1
30 to 39 years	120	11.9

The College draws both its staff and students from the whole of China, and demands in them a high grade of previous education. Instruction and departmental correspondence is conducted entirely in the English language. With the exception of the graduate nurses only, who may have received their education in small country schools, all those included have undergone several years of instruction in schools of such standing as to be found only in the larger cities of China. The material studied, therefore, represents as complete a cross-section of the educated young adult population of China as it would be possible to collect. That it is, as far as possible, a selection of the "healthy" population is evidenced by the fact that a medical certificate of physical fitness must accompany each application in the case of candidates coming from a distance.

On arrival each individual is given a thorough physical examination by a member of the College Health Staff, all of whom have special experience in such routine examinations. Any individual showing definite signs of pulmonary disease at this examination has been excluded from this series.

X-RAY DIAGNOSIS

All films were reviewed by both authors together. The individual was placed in one of the following categories (1) on the basis of the findings in the first X-ray films:

1: No evidence of tuberculous lesion.
2: Pulmonary nodule: Calcified foci in the peripheral lung field, without significant calcification in the tracheobronchial lymph nodes.
3: Tuberculosis of tracheobronchial lymph nodes: Visible calcium deposits within the hilum shadow, estimated to cover an area of 1 sq. cm. or more. A pulmonary nodule is not recorded in this category.
4: Latent nonapical pulmonary infiltration: Lesions occurring in the infraclavicular region, and parenchymal involvement in the hilar and midlung regions, and occasional basal lesions, when there seemed to be enough evidence to show them to be tuberculous, are included in this category, provided always that their appearance is such as to suggest quiescence, if not complete healing.
5: Latent apical infiltration: Lesions of the same character as those in category *4* but occurring in the apical areas. Such lesions generally give the appearance of being well-healed apical scars.
6: Manifest tuberculosis: All pulmonary infiltrations definitely tuberculous in character with the appearance of activity as seen in the X-ray films. It must be remembered that, though these lesions are called "manifest," in no case were they giving rise to symptoms of ill-health appreciable to the patient, nor were they producing physical signs discoverable by a physician with special experience in conducting physical examinations. Individuals in this category were, therefore, suffering from pulmonary tuberculosis which was still "latent," though at the same time active, and therefore very definitely in need of treatment.

RESULTS

The original diagnoses made from the stereoscopic X-ray films of the lungs of the 1,007 individuals are summarized in table 1.

Infection incidence: The results show that 81 per cent of healthy young Chinese adults show definite evidence within the thorax of infection with tubercle bacilli. It is unfortunate that parallel tuberculin-testing was not done, as more accurate information might have been forthcoming as to the importance to the individual of such an infection.

One is justified in assuming that, with evidence of such a high incidence of infection, a high percentage of positive reactions to tuberculin would be found. Of 331 intracutaneous tuberculin tests, done in the months of January to July, 1930, on adult male Chinese of the artisan

TABLE 1

Results of X-ray examination

CATEGORY	NO EVIDENCE OF TUBERCULOSIS			CALCIFIED PULMONARY NODULE			TUBERCULOSIS OF TRACHEOBRONCHIAL LYMPH NODES			LATENT SUBAPICAL LESION			LATENT APICAL LESION			"MANIFEST" TUBERCULOSIS			TOTALS	
	Number		Per cent	Number		Per cent	Number		Per cent	Number		Per cent	Number		Per cent	Number		Per cent		
Medical students	M—21 F— 9	30	16.3	M— 9 F— 4	13	7.1	M— 89 F— 22	111	60.3	M— 4 F— 1	5	2.7	M—10 F— 1	11	6.0	M—13 F— 1	14	7.6	M—146 F— 38	184
Nursing students	M— 0 F— 8	8	14.8	M— 0 F— 0	0		M— 0 F— 41	41	75.9	M— 0 F— 1	1	1.8	M— 0 F— 2	2	3.7	M— 0 F— 2	2	3.7	M— 0 F— 54	54
Physicians	M—22 F— 2	24	13.9	M— 1 F— 1	2	1.2	M— 87 F— 15	102	58.9	M— 9 F— 1	10	5.8	M—22 F— 2	24	13.9	M—10 F— 1	11	6.4	M—151 F— 22	173
Nurses	M—20 F— 78	98	21.9	M— 2 F— 19	21	4.7	M— 55 F— 200	255	57.0	M— 2 F— 16	18	4.0	M— 7 F— 19	26	5.8	M— 5 F— 24	29	6.5	M— 91 F— 356	447
Nonprofessional staff	M—11 F— 13	24	21.8	M— 6 F— 3	9	8.2	M— 35 F— 24	59	53.6	M— 4 F— 2	6	5.4	M— 1 F— 5	6	5.4	M— 5 F— 1	6	5.4	M— 62 F— 48	110
Graduate students	M— 6 F— 0	6	15.4	M— 1 F— 0	1	2.6	M— 21 F— 4	25	64.1	M— 4 F— 0	4	10.2	M— 2 F— 0	2	5.1	M— 1 F— 0	1	2.6	M— 35 F— 4	39
Totals		190	18.9		46	4.6		593	58.9		44	4.4		71	7.1		63	6.3	M—485 F— 522	1,007

M = male; F = female.

class in the employ of the Peiping Union Medical College, 94.25 per cent gave a positive reaction to a dilution of 1:1,000 (0.1 mgm.). Only three individuals, however, showed a strong reaction with vesiculation (personal communication from Dr. C. L. Tung). Korns (2), using various techniques, found a surprisingly small percentage of reactors to tuberculin among school-children and inmates of charitable institutions in and around Peiping. His series included children from 8 to 20 years, and the percentage of positive reactors ranged from 17 at 8 years to 49 at 20 years. In a further effort to estimate the incidence of tuberculosis, Korns in 1928 (3) examined the material available from the first 500 cases coming to autopsy in this hospital. Of the autopsies on suitable Chinese individuals only 38 per cent gave evidence of healed or active tuberculous lesions, and in 29 per cent only were calcified lesions found. No special technique was used in looking for healed and calcified lung lesions, and only the routine autopsy procedure was followed.

Calcification in tracheobronchial lymph nodes: The presence of a considerable deposit of calcium in the lymph nodes at the hilum of the lung in otherwise normal young adults is usually considered to represent a tuberculous infection in childhood. If the individuals in our series who have pulmonary infiltrations are excluded (the presence of calcium in the hilum in such cases was not recorded) 71.5 per cent of those remaining show this evidence of childhood infection.

The Phipps Institute studies show a considerably smaller number of individuals with such evidence of childhood infection. Philadelphia children of high-school age (12 to 20 years) gave an incidence of about 15 per cent (4), college students 10 per cent, and medical students 14.2 per cent (1).

Herman (5), however, found 63 per cent of 278 medical students of the Johns Hopkins Medical School to show calcium deposits. It is interesting to note further that 57.9 per cent of his students, who failed to react to tuberculin in a dilution of 1:1,000 (0.1 mgm.), showed such evidence of childhood infection.

The anatomical studies of Scott (6) and Minett (7) in Hongkong show how almost invariably are the lungs involved when there is any tuberculous infection in the Chinese. They conclude on the basis of this work that the respiratory system is the portal of entry for the tubercle bacillus in almost every case. The fact that a very high percentage of their material was obtained from children under 10 years, an age at which extrapulmonary lesions would be expected to predominate in any Euro-

pean or American series, makes their findings all the more significant. The absence of any evidence of bovine tuberculosis in China, and the fact that cow's milk is still but little used in infant nutrition, are possible explanations for this finding.

Latent disease: It would seem that tuberculosis must have been widely endemic in China in the days of her old civilization, since clinical experience shows that it now produces a localizing, well-restricted type of

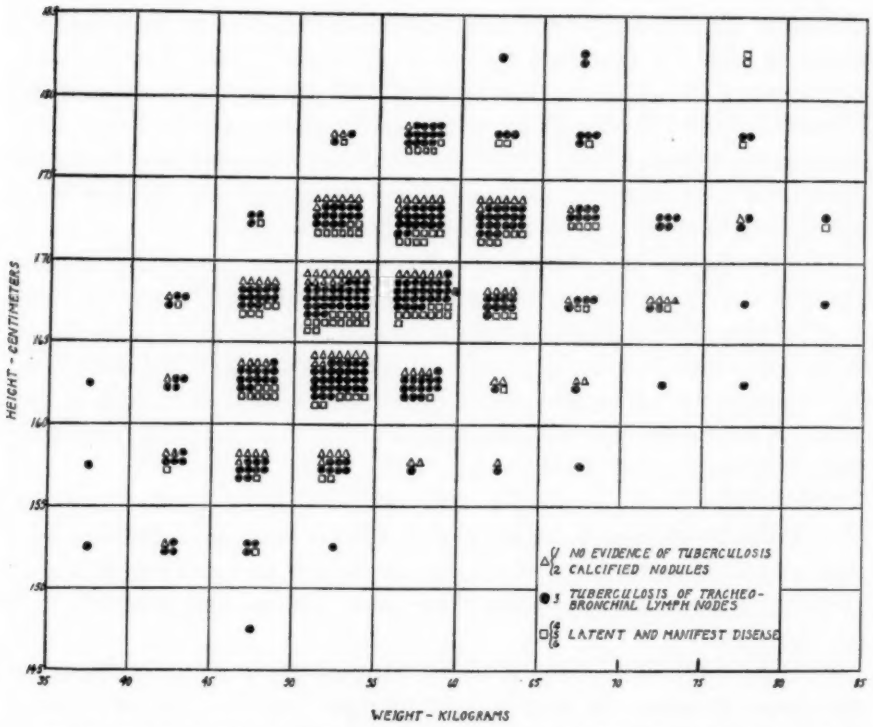
HEIGHT - CENTIMETERS
WEIGHT - KILOGRAMS
1 NO EVIDENCE OF TUBERCULOSIS
2 CALCIFIED NODULES
3 TUBERCULOSIS OF TRACHEO-BRONCHIAL LYMPH NODES
LATENT AND MANIFEST DISEASE

FIG. 1. Showing height and weight of 483 male Chinese with (1) no important tuberculosis; (2) tuberculosis of tracheobronchial lymph nodes; and (3) latent and manifest disease.

disease, and that few bacilli are found in the sputum. Infection appears to be universal and inevitable, but infecting doses are small, even though frequently repeated. Under these circumstances immunity is maintained at a high level, though allergy is not unduly raised, or, having been high, is reduced by the subsequent small infections (compare the experimental work of Krause and Willis (25)) and latency of lesions might well be expected.

Our results show that no less than 17.8 per cent of "healthy" young Chinese adults are suffering from latent pulmonary tuberculosis, and that 6.3 per cent of them have lesions which demand immediate treatment, in spite of complete absence of symptoms.

It is interesting to note in passing that, as a group, those showing latent and "manifest" disease (categories *4*, *5* and *6*) show no marked difference in the relation of weight to height compared to those with no

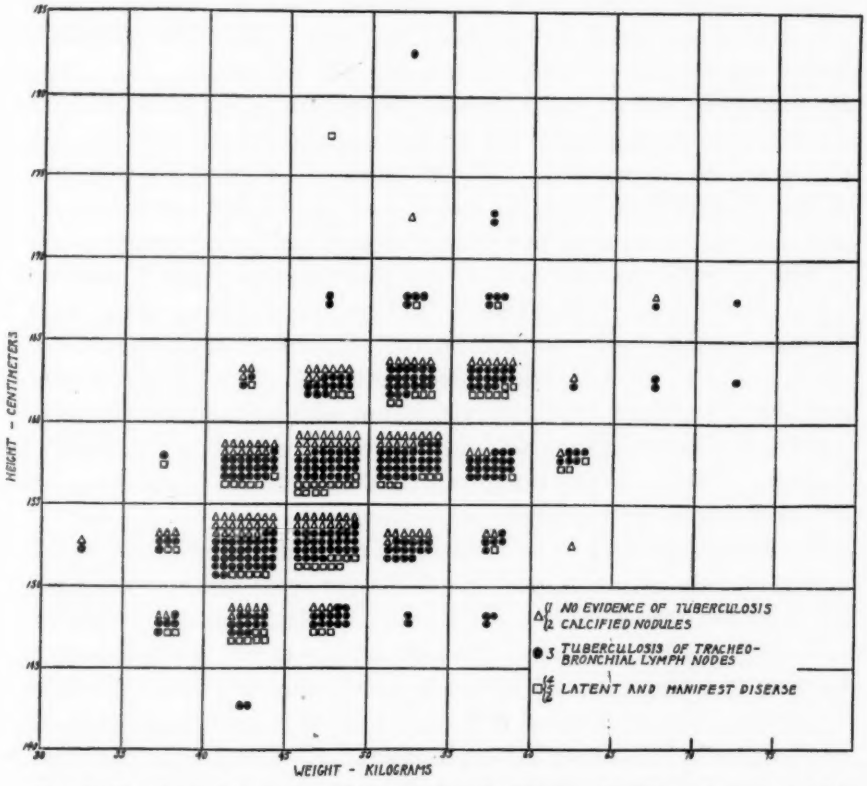
HEIGHT - CENTIMETERS
WEIGHT - KILOGRAMS
1, 2 NO EVIDENCE OF TUBERCULOSIS CALCIFIED NODULES
3 TUBERCULOSIS OF TRACHEO-BRONCHIAL LYMPH NODES
4, 5, 6 LATENT AND MANIFEST DISEASE

FIG. 2. Showing height and weight of 529 female Chinese with (1) no important tuberculosis; (2) tuberculosis of tracheobronchial lymph nodes; and (3) latent and manifest disease.

evidence of important tuberculosis (categories *1* and *2*) or those with tracheobronchial adenitis (category *3*), as shown in figures 1 and 2.

Anderson (8), after examining 1,600 Chinese by "light percussion and anamnesis," estimated the rate of "latent and incipient phthisis" in West China to be about 21 per cent. His series included students of the West China Union University and Senior Middle School, as well as clinic and hospital patients.

Recent American and European statistics are available for comparison with these figures. Hetherington and others of the Phipps Institute (1) found latent or manifest pulmonary tuberculosis in 9.8 per cent of college and medical students at work in the University of Pennsylvania. Kattentidt (9), as a result of fluoroscopic examinations of 4,836 students in the University of Munich, found 2 per cent suffering from "significant" latent tuberculous infection. Another 14.8 per cent were said to have inactive latent lesions; 0.56 per cent had "active" disease. Special efforts have been made by the Yale University Department of Health to detect tuberculosis in students entering the University (10). During the year 1930–1931 routine X-ray examinations were made on all entering students, numbering 1,644, equally divided between the undergraduate and graduate departments. Of this number 1.8 per cent were found to have "latent" lesions, either apical or subapical, and a further 14.4 per cent showed calcification in the tracheobronchial lymph nodes.

Prognosis: In the case of 308 individuals subsequent X-rays were taken after periods varying from 3 to 110 months. Those whose original diagnosis was that of "manifest disease" all received some form of treatment, many of them artificial pneumothorax. The remainder stayed on full duty, under special supervision, but without treatment except the administration of codliver oil when nutrition seemed to be below the average. Table 2 shows the change in diagnosis and the average time, in months, required to produce such change.

It will be seen that of 62 individuals originally showing no evidence of tuberculosis in their X-ray films 5 (8.1 per cent) had developed manifest disease after an average of $5\frac{1}{2}$ years. Only 7 persons (11 per cent) had developed hilum calcification without any parenchymal lesions, and 4 others (6.4 per cent) had produced latent parenchymal infiltrations.

Manifest disease occurred with almost equal frequency amongst those who originally had latent lesions, namely, 4 of 48, or 8.3 per cent, but in about half the time, namely, in an average of 25.7 months.

Manifest disease developed less frequently in those who started work in the hospital with calcification of the lymph nodes as the only evidence of a prior infection. Only 6 of 144 such individuals (4.1 per cent) developed active disease after the expiration of an average of 54.5 months.

It would seem, therefore, that deposits of calcium in the hilum signify some degree of protection to the individual possessing them. Latent lesions are liable to "break down" and produce manifest disease about as frequently as unprotected individuals develop active lesions, but in a

TABLE 2

Showing change of X-ray diagnosis in 308 cases, and average time, in months, required to produce such change

ORIGINAL DIAGNOSIS		FINAL DIAGNOSIS											
		No evidence of tuberculosis		Calcified pulmonary nodule		Tuberculosis of tracheobronchial lymph nodes		Latent subapical lesion		Latent apical lesion		Manifest tuberculosis	
		Number	Time	Number	Time	Number	Time	Number	Time	Number	Time	Number	Time
No evidence of tuberculosis	62	46	40.7	0		7	43.1	1	53	3–4.8%	52.7	5–8.1%	66.4
Calcified pulmonary nodule	16	0		13	59.7	3	33.7	0		0		0	
Tuberculosis of tracheobronchial lymph nodes	144	0		0		137	39.5	0		1	65	6	54.5
Latent subapical lesion	16	0		0		0		14	20.6	0		2	31.0
	48											4–8.3%	25.7
Latent apical lesion	32	1	51.0	0		0		0		29	29.3	2	20.5
Manifest tuberculosis	38	0		0		0		1	22	6	67.7	31	34.2
Totals	308	47		13		147		16		39		46	

shorter period of time; and this occurrence is about twice as frequent as the development of active disease in "protected" individuals.

Professional hazard: Considerable interest is now aroused in Western countries in the apparently heightened incidence of pulmonary tuberculosis in doctors, nurses, and sanatorium workers. Jacquerod (11) produces no statistics, but gives warning and instructions to internes concerning the necessity and method of avoiding this professional hazard. Steidl (12), from answers received from 579 law graduates and 556 graduates of the Medical School of Harvard University, found that active pulmonary tuberculosis developed in as many nonmedical as medical men within the first ten years after graduation.

A definitely low incidence (less than 2 per cent) of tuberculous disease was found in 737 past workers in the Chest Service of the Jefferson Hospital (13). Heimbeck (14), Geer (15), and Myers (16) all emphasize the risk run by nurses in general hospitals, and show that those with negative tuberculin reactions are particularly liable to develop clinical tuberculosis after comparatively short periods of duty. Ross (17) found that 6 per cent of 800 Canadian trained nurses became sanatorium patients during training, or within one year of graduation, and that $6\frac{1}{2}$ per cent of all female patients in 13 different sanatoria were nurses.

Herman (5), working with data from the Health Services of the Johns Hopkins, Michigan, and Western Reserve Universities, passes the Scottish verdict of "not proven." He admits, however, that "if a medical student is negative to tuberculin on enrolment, he is practically certain to be positive before completion of his third year, and that an allergic student is likely to become more sensitive." The Henry Phipps Institute has turned its attention to this problem, and its studies show an increasingly higher incidence of latent and manifest disease with each succeeding year of medical study in the University of Pennsylvania (1). Of 279 college students, 3.9 per cent were found to have latent or manifest lesions, and 10 per cent tracheobronchial adenitis, whereas of 122 medical students in their 4th year, 21 per cent had pulmonary infiltrates either active or latent, and 13 per cent calcification at the hilum. The Yale figures (10) show that 4.5 per cent of 44 graduate students in the department of medicine had latent lesions. This figure is not significantly higher than the average for the whole graduate-school (3.1 per cent), and is about the same as that for the 122 graduate students of the school of divinity (4.1 per cent).

The professional hazard is not strongly accentuated in our figures

(see table 3). The highest incidence (26 per cent) for latent and manifest disease is found in the group of physicians. The disease incidence for nurses (16.3 per cent) is, however, below that for the whole series (17.8 per cent), and is almost the same as that in the nonprofessional group (16.7 per cent).

It is legitimate to argue, we think, that in China widespread infection keeps immunity at a high level, and the hazard of reinfection is not so great as it is in countries where immunity is not acquired or maintained, owing to the absence or the complete healing of an early infection, and

TABLE 3

Results of X-ray examinations of various groups with percentage showing each type of tuberculous lesion

GROUP	AVERAGE AGE	CALCIUM IN TRACHEOBRONCHIAL LYMPH NODES		PULMONARY TUBERCULOSIS			
		Number examined	Per cent	Number examined	Latent subapical per cent	Latent apical per cent	"Manifest" per cent
P. U. M. C. students	22.0	203	74.3	238	2.5	5.5	6.7
Pennsylvania students	19.5	279	10.0	279	0.36	3.1	0.36
Yale undergraduates	18.8	849	12.0	849	0.11	0.66	0
P. U. M. C. physicians	28.6	128	80.0	173	5.8	13.9	6.4
Penna. 4th-year medical students	24.3	122	13.1	122	0.82	13.0	7.3
Yale medical students	21.1			44	2.25	2.25	0
P. U. M. C. nurses	24.5	374	68.1	447	4.0	5.8	6.5
P. U. M. C. nonprofessional	26.5	124	67.7	149	6.7	5.4	4.7
P. U. M. C.: all cases	24.9	829	71.5	1007	4.4	7.1	6.3
Pennsylvania; all cases	21.4	731	13.6	731	0.41	7.4	2.0
Yale: all cases	21.7	1644	14.4	1644	0.6	1.0	0.18

the absence of further small reinfections. The high incidence of latent *apical* lesions (13.9 per cent) among Chinese physicians, which, more than active lesions, is responsible for raising the disease incidence to its high level, shows that exogenous infections are well resisted and tend to heal. This would seem to be a corollary to the findings of Heimbeck, Geer, and Myers, that the development of active disease is frequent in nurses entering training with negative tuberculin reactions, and that the disease tends to be acute and of an allergic nature.

Racial type: The experimental work of Paul Lewis and Dorothy Loomis (18) shows that by inbreeding guinea pigs family differences in reaction

to infection with the tubercle bacillus can be produced. Before it can be said, however, that differences in reaction occur in the various races of mankind, the environmental factors which influence tuberculous infection must be considered. The acute forms of tuberculosis met with in the French native troops during the war, and described by Borrel (19), do not represent a different racial reaction to the tubercle bacillus, but rather the reaction of a specifically nonimmune individual, such as an infant in more "tuberculized" communities.

The intensive studies of the committee investigating the cause and nature of tuberculosis in South African gold mines (20) show that though strongly allergic to tuberculin (48.6 per cent of raw natives react to tuberculin in a dilution of 1 to 10,000,000), native boys have but little specific immunity to tuberculosis. A higher incidence of disease is found to occur after arrival at the mines in those that have a positive (particularly a strongly positive) reaction to tuberculin, than in those that fail to react to tuberculin. Infection occurs in the villages, and is received in massive doses seldom repeated. The "large dose" infection creates a high sensitivity accompanied by but little specific immunity, and, though kept in check under the natural conditions of a kraal life spent in the open air and sunshine, breaks the barriers of resistance when its host is exposed to the unnatural conditions of work in a mining-camp, and then produces an active nonlocalizing, rapidly fatal disease. Many of the boys developing tuberculosis die in the camp hospitals. A few return home, and before death infect their contacts with a "large dose" similar to that responsible for their own first infection.

Opie (21) found a very similar type of disease among native Jamaicans, and showed that the bacilli eliminated in the sputum in such cases occurred in far greater numbers than in patients suffering from the more chronic forms of tuberculosis seen in Europe and in the United States. Unfortunately general tuberculin-testing was not done, and so the state of allergy in this community is not known.

Members of the Negro race in America suffer in a different degree and more severely from tuberculosis than does the white population with which they live in contact, but Opie (22) finds no evidence to show that they have any "racial susceptibility" to the disease.

Max Pinner (23) has recently studied the differences in type and distribution of tuberculous lesions in white and Negro patients coming to autopsy. After acknowledging and discussing the rôle that environmental conditions play in producing these differences, he inclines to the

view (which, however, he admits he is unable to prove) that a true "genotypic" difference between the two races does exist. He states that the Negro responds to infection with a higher degree of allergy, which cannot be called a sign of true immunity. He further admits that tubercle bacilli are found in greater numbers in Negro homes with open cases of tuberculosis (Augustine (24)), but discusses "massive infection" only in its relation to disease production, and not as a factor in producing high allergy without corresponding immunity or resistance to disease.

He states that large infections must mean frequently repeated infections. Though this may be true in Negro households in America, it does not represent the state of affairs in the South African villages, where the early death of the bacillus-producer, and the destruction of his hut and belongings after his death, rapidly clears the contaminated environment. It is improbable that those whom he has infected during his life will again come in contact with bacilli in either large or small numbers until they leave their kraals to join the mining camps. The thorough work of the South African Commission has shown that an extremely allergic state is produced in such contacts, but with it, a lessened rather than an increased immunity to disease. A different state would seem to be produced where first infections are small, and such small infections are constantly and frequently repeated, as is liable to occur in those in contact with a patient suffering from a chronic form of tuberculosis, producing, over a long period of time, small numbers of bacilli. The small reinfecting doses act as doses of tuberculin, and desensitize the individual in contact, making him less allergic, but keeping his immunity constantly at a high level. This, we feel, is what Krause and Willis (25) showed by their animal experiments, and is what they meant when they summarized their findings in the following words, "Allergy and immunity respond to infection in two opposite ways, as factors of quantity and time of reinfection move toward one or other end of a scale."

Theobald Smith has suggested that the tubercle bacillus tends to adapt its virulence to the resistance of its host, so that it may produce a long-continued disease favorable to dissemination. To this Opie (26) adds that, with widespread latent infection, virulence might be modified to produce long-continued disease in a partially immunized host. When such disease exists, bacilli are produced in smaller numbers than in the case of the more acute forms, and over a longer period of time. In this way, if our contention is correct, those in contact with patients with this

type of disease will lose much of their sensitivity to tuberculin, and yet maintain a high state of immunity.

Neander (27) has shown how, in certain isolated communities in Sweden, as tuberculosis became more diffusely endemic, it changed from an acute, progressive and malignant disease, with a high mortality, to assume a more chronic, localizing form, with a higher morbidity rate but lower mortality. A high and increasing mortality rate is found for about a century (three generations) from the time that the disease first enters a new community, and after this period the mortality falls rapidly.

Anderson (28), from a study of tuberculosis in the Island of Mauritius, states that a native race, when it comes in continual contact with the disease, begins to acquire resistance in 30 years, has acquired it to an appreciable extent in 50 years, and in more than 100 and less than 200 years has developed resistance to the full (European) degree.

History is thus able to teach us that tuberculosis, as well as the tubercle bacillus, is able to adapt itself so as to ensure its continuation within a race, and that a newly tuberculinized race will react at first like an infant, later like a child and finally like an adult of the more ancient civilizations. No genotypic peculiarities in reaction to the disease, and no change in environment are necessary to explain these differences. No community of any size, however "susceptible," has ever been completely decimated by tuberculosis, and probably this will never occur. The continued presence of the disease, and its bacilli, in the community, the gradual reduction of an extreme allergy (which is at first the penalty paid for immunity), as more and more individuals withstand their early massive infections, gradually change the type of disease seen in adults of the race, until finally a chronic, nontoxic, long-latent disease becomes widely diffused throughout the population.

Our experience would suggest that China has reached this late stage in her tuberculosis history, and is further along the road than any other race. The disease has developed in an essentially isolated community, along natural lines and with a complete absence of any conscious effort at control, and so represents the ultimate development or adult stage of tuberculosis in any community. We show here how universal is infection; that allergy is not unduly high, though immunity is well maintained, and exogenous reinfection well resisted. The disease remains latent for a long time and until it is widespread. Symptoms are mild, disturbance of metabolism and nutrition are not marked, and physical signs are scanty. Response to treatment is slow, and relapse frequent. That

this type of disease is one eminently suited to its survival and dissemination is obvious. That it represents an extremely undesirable state of affairs for the community in which it exists is apparent to any intelligent worker in China to-day. It is the keen and energetic adolescent, struggling against long odds to improve himself and his environment, that it chooses for its victim. It allows the indolent, pleasure-loving opium-smoker to continue to enjoy his existence, while producing a constant stream of bacilli to infect his grandchildren, with whom he loves to play.

Many of the ills from which China to-day suffers arise from the present nature of her tuberculous infection.

SUMMARY AND CONCLUSIONS

1. The X-ray findings of the lungs of 1,007 "healthy" young Chinese adults are reported.

2. A high incidence of early infection (71.5 per cent), as shown by calcium deposits within the hilum shadow, is found.

3. Latent disease is found in a larger percentage of young Chinese adults than in Westerners of approximately the same age and social status.

4. More than 6 per cent of latent lesions have the appearance of activity, as seen in X-ray films.

5. There is not sufficient evidence to prove that Chinese doctors and nurses suffer any increased hazard from exposure to patients suffering from pulmonary tuberculosis.

6. Active disease develops no more frequently in individuals who have well-healed latent pulmonary tuberculosis, than in those who show no evidence of tuberculous infection in their X-ray films.

7. There is no evidence to show that there is any "genotypic" racial difference in reaction to infection between Chinese and members of other races.

8. It is concluded that such differences in reaction to infection as are found between members of different races can be explained by different lengths of contact with the tubercle bacillus.

9. It is suggested that, by reducing allergy while maintaining a high degree of immunity, frequently repeated infections play a large part in altering the character of the disease as it becomes diffused through any community.

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ACID-FAST AND NON-ACID-FAST MICROÖRGANISMS IN SKIN NODULES OF TUBERCULIN-REACTING CATTLE[1,2]

LYMAN L. DAINES AND HAROLD AUSTIN

Cattle in Utah which are condemned and slaughtered because of reacting to the tuberculin test fall into three groups: (1) those in which gross lesions of systemic tuberculosis are found on postmortem examination, about 8 per cent; (2) those showing only "skin lesions," about 60 per cent; and, (3) those in which no gross lesions and, so far, no microscopic lesions are found, about 32 per cent.

Serious doubt has recently been expressed by many as to the tuberculous nature of the skin nodules of these tuberculin-reacting cattle. However, acid-fast microörganisms are found routinely in their lesions if careful search is made for them, and we have been able to obtain cultures of these acid-fasts in a large percentage of cases. In addition to these it is possible in nearly all cases to find, by direct smears and also by cultural methods, non-acid-fast microörganisms which are morphologically similar to the acid-fast forms. These non-acid-fast strains often show acid-fast properties which vary greatly in different cultures. Because of the almost constant association of these acid-fast and non-acid-fast strains and also because of other evidence which will be given in a later section of this paper, the question constantly presents itself as to whether or not these forms represent different phases in the life-cycle of the same organism. It might be pointed out in the beginning that this question cannot be fully answered with the evidence at present available, but it is probably worth while at this time to mention a few observations that have recently been made.

Previously we (1) concluded that our organism is one of the following:

(1) a modified Preisz-Nocard or similar organism, or
(2) an actinomyces similar to, or identical with Walker's strains obtained from human and rat leprosy, or

[1] From the University of Utah, Salt Lake City, Utah.

[2] Presented at a session of the Pathological Section at the twenty-ninth annual meeting of the National Tuberculosis Association, Toronto, Ontario, June 28, 1933.

(3) stages in the life cycle of an attenuated mammalian or avian tubercle bacillus, or
(4) contaminating acid-fast and non-acid-fast saprophytes, or
(5) an undescribed species.

We also expressed an opinion that the evidence indicates that the organism is not *Mycobacterium tuberculosis*.

The results obtained since our previous reports still tend to confirm this conclusion, and we believe that the evidence continues to indicate the probability that we are dealing with an undescribed form either of an actinomyces or a mycobacterium.

We arbitrarily classified the organisms recovered by us from the skin lesions into four groups as follows:

(1) an occasional *Mycobacterium tuberculosis bovis;*
(2) a non-acid-fast and partially acid-fast, pleomorphic, and usually chromogenic, bacillus;
(3) an acid-fast, bacillary, pleomorphic, orange-colored chromogen;
(4) a non-acid-fast, nonchromogenic, pleomorphic bacillus.

We have recently obtained cultures directly from skin lesions in fresh uncooked egg-yolk. Before planting, the ground-up material from the lesions was treated for 20 minutes with 6 per cent sulphuric acid. In six days, at room temperature, non-acid-fast and acid-fast pleomorphic forms appeared. All of these soon became strongly acid-fast when transferred to Petroff's egg medium, produced the characteristic deep orange color of our group 3, and have continued with the characteristics of this group. This method reduces the time necessary for isolation, and otherwise simplifies the recovery of these organisms in pure culture.

Several cows have developed what seem to be typical "skin lesions" after receiving repeated subcutaneous inoculations of our group-3 organism. One animal has now been under observation for 22 months. The lesions in this case seem to be slowly progressing, and they still contain what seem to be organisms of the third group. This cow and one other have given rather definite but transitory tuberculin reactions, and they have given pronounced allergic reactions when injected with a protein filtrate of group-3 cultures. This filtrate is now being tried out in animals that respond to the Bureau of Animal Industry tuberculin, especially in "skin-lesion" cases.

Such a large amount of work has been done in recent years with the

acid-fast organisms, on the problems of the developmental-cycle and single-cell dissociation, that we shall not attempt to mention the voluminous literature in this brief paper. Extensive bibliographies are given in recent papers by Kahn (2), Kahn and Schwarzkopf (3), Sweany (4), Miller (5), Lohnis (6), Petroff and Steenken (7) and others. Many reports of great interest have appeared from the time of the pioneer work of de Kruif (8) and Hadley (9) to the latest paper of Mellon's (10). We consider it unnecessary at this time to repeat these facts. We shall mention very briefly some of the observations recently made in connection with our cultures, which might have some bearing on the above-mentioned phenomena.

Our group-4 strains were passed in rapid succession on a glycerol-agar medium for 10 transfers and then plated on bovine kidney-and-liver-hormone-media. What seem to be typical group-3 organisms as well as those of group 4 developed. They have retained in subculture the typical chromogenic, morphological and staining characteristics of the respective groups. Further work is being done with these strains in an attempt to determine whether or not they represent true dissociation strains.

Group-2 non-acid-fast cultures were kept on Petroff's egg medium for six weeks in a gas chamber containing 10 per cent carbon dioxide, 40 per cent oxygen and 50 per cent air. Several acid-fast, deep-orange colonies developed, from which we have obtained what appear to be pure cultures of organisms which have the morphological and colony characteristics of our group-3 acid-fast strains.

Group-3 seedings on Sweany's egg medium continued without visible growth for eight months. They were then covered with sterile paraffin oil, and there soon developed on the portion of the slants, which had been streaked, cultures which have the characteristics of our group-2 organisms. This suggests a possible anaerobic stage between our group 3 and group 2.

Several times the inoculation of group-2 strains into guinea pigs has been followed by the recovery of acid-fast organisms which seem to belong to group 3. Others report similar results with our cultures. In one case only the inoculation of group-3 organisms was followed by the recovery of cultures which appear to be identical with group-2 strains.

Group-2 cultures are typically rough and dry, but we have been able to secure dissociation into smooth colonies. Group-3 cultures are smooth and moist. A few attempts to obtain dissociation have all been unsuccessful. We hope to be able to induce dissociation in this group.

In the bovine lesions we find acid-fast and non-acid-fast organisms together in almost every case. This is true even in lesions which give no visible evidence of connection with the surface of the skin. The lesions themselves are large enough and are of sufficient thickness to make possible the obtaining of cultures from the interior without adding contaminations from the outside at the time the cultures are made.

We have attempted to obtain evidence from other conditions than bovine skin lesions as to possible association of acid-fast and non-acid-fast organisms.

Thus repeated cultures of sputum from human tuberculosis patients have yielded pleomorphic coccoid, streptococcoid, diphtheroid and solid bacillary non-acid-fast and partially acid-fast organisms which are morphologically and culturally similar to our group-2 strains from bovine skin lesions. On rich media these organisms have developed fairly strong acid-fast properties.

From 477 cultures made from human leprosy nodules and from post-mortem material we have obtained 160 cultures of acid-fast organisms. Of these, 104 seem to be pure cultures and the remainder contain, in addition to the acid-fast organisms, non-acid-fast or partially acid-fast very pleomorphic forms. These latter forms have a remarkable resemblance to the diphtheroids isolated by Walker (11) from the lesions of human leprosy and by Walker and Sweeney (12) from rat leprosy. They also exhibit a close similarity to the non-acid-fast or partially acid-fast organisms isolated by us from bovine skin lesions and from sputum from human tuberculosis.

DISCUSSION

The evidence presented cannot be considered as conclusive in proving the specific relationship between our acid-fast and non-acid-fast strains. We are aware that our cultures may be mixed, although, with the exception of single-cell-isolation technique, we have used every precaution we could to ensure the purity of our strains. We are now attempting to check our results with single-cell cultures. Even with this method the question of the possible presence of ultramicroscopic forms of contaminating organisms will always be on hand to vex us.

The chances of either a contamination through the skin or in some other way of a true commensalism must be kept in mind. The rather constant presence of diphtheroids on the skin, and on many mucous membranes

connected with the skin, offers unquestioned possibilities of the entrance of these organisms into lesions, especially superficial ones.

Results obtained from animal inoculations strongly point to the probability that the group-3 organism is the cause of the spontaneous skin lesions in cattle and also of the tuberculin sensitiveness in the tuberculin-reacting animals having these lesions.

The tuberculin reactions in our experimental animals offer a very close resemblance to the reactions observed in spontaneous cases in routine field work. The temporary nature of the reaction is often noted by field workers and has been experimentally recorded recently at the Wisconsin Agricultural Experiment Station (13).

SUMMARY

Further evidence is submitted tending to confirm our previous view as to the aetiological relationship between our group-3 organisms and spontaneous skin lesions in tuberculin-reacting cattle.

A new method is reported which simplifies the recovery of group-3 organisms in pure culture from the lesions.

Evidence is given which indicates the possibility of a non-acid-fast as well as an acid-fast stage in the life-cycle of our organism.

Evidence is also presented of a possible similar relationship between acid-fast and non-acid-fast forms in human tuberculosis and human leprosy.

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QUANTITATIVE TESTS ON 944 TUBERCULOUS ADULTS WITH TPT (SEIBERT)[1]

M. R. LICHTENSTEIN[2]

Quantitative intracutaneous tests with TPT were performed on practically all the adults in the Chicago Municipal Tuberculosis Sanitarium within a period of a few weeks, with a view to determining, first, the reliability of the product; second, percentages of sensitive and nonsensitive patients; and finally to analyze the relation of the level of skin sensitivity to various associated factors.

Tuberculin: TPT (Seibert) (1), the precipitated skin-reactive protein fraction from synthetic-medium tuberculin was kindly furnished by Dr. Seibert for these tests and was used exclusively. This product is standardized, so that future tests may be performed with other batches and accurate quantitative comparisons made.

Dilutions: One original batch of TPT powder made up 10 mgm. per cc. was used throughout. This is called the 1:1 dilution and is equivalent to undiluted O.T. The comparative potency was verified for O.T. (Parke, Davis & Co.) by quantitative tests run on the two arms of a group of patients. Further dilutions 1:10; 1:100; 1:1,000; and 1:10,000 were made each week and kept on ice. No preservatives were used.

Dose: The volume of each injection was 0.05 cc. measured carefully from a 1-cc. tuberculin syringe. This volume is the same as used by Mariette (2), *et al.*, but is half of the usual volume used in tuberculin testing. The smaller volume injection was used because it is less painful and is less likely to be partially lost by subcutaneous injection, or back-pressure leakage about the needle. The large-volume injection has been given up by allergists in favor of 0.02- to 0.05-cc. quantities, and the same tendency should prevail in tuberculin testing. To compare the relative size of reactions with 0.05 cc. and 0.1 cc. of the same dilution on the same patient a series of 25 patients was thus tested. The smaller volume averaged transverse diameters two-thirds of the larger, and in only one case did it fail to react when the larger showed a small positive reaction.

[1] From the Municipal Tuberculosis Sanitarium, Chicago, Illinois.
[2] Rush Medical College, Chicago, Illinois.

Methods: It was attempted to obtain a cross-section analysis of the total Sanitarium population at one time. Of approximately 1,000 adults, 971 were tested. The remainder were missed because of various causes, including absence on passes and refusals. Seventy-five to 100 patients were tested each day, and practically all were finished within 3 weeks.

The 1:10,000 and 1:1,000 dilutions were first used on all patients. Readings were made in 48 hours in all cases and the transverse diameters recorded. If no reaction was observed, the 1:100, 1:10 and 1:1 dilutions were used at 48-hour intervals until a reaction was obtained or all were tried.

In the results of the 1:10,000 dilution tests, results are given as positive or negative to avoid confusion. The 1:1,000 dilution is given as + to

TABLE 1

	TUBERCULOUS	NONTUBERCULOUS	TOTAL
Neg. 1:10,000	223	14	237
Pos. 1:10,000	721	13	734
+ 1:1000	655	13	668
++ 1:1000	197	1	198
+++ 1:1000	62	3	65
++++ 1:1000	8	0	8
Pos. 1:100	13	3	16
Pos. 1:10	2	0	2
Pos. 1:1	0	2	2
Neg. 1:1	2	5	7
Unfinished	5	0	5
Total	944	27	971

++++ in the usual manner; (+, less than 1 cm.; ++, 1 cm. to 1.5 cm.; +++, over 1.5 cm.; and ++++, vesiculative or necrotic reactions). The other dilutions are given as positive or negative.

Analysis: Because of the unusually high quality of the clinical and laboratory work done at the Sanitarium, very complete data concerning each case were available. The scepticism of the staff concerning the diagnosis of observation cases has resulted in careful elimination of nontuberculous patients or their correct labelling. The data presented in regard to diagnosis, complications, and associated diseases may therefore be considered as nearly correct as is possible.

Total number of patients tested: Table 1 shows general data on 971 patients tested (479 male and 492 female), of whom 27 were diagnosed

as nontuberculous. The latter are omitted from further consideration, as this analysis concerns the percentage of error in testing known tuberculous patients. The diagnosis in practically all the tuberculous patients was verified beyond any reasonable doubt by positive sputum, cultures

TABLE 2

	PER CENT POSITIVE IN 944 ADULT PULMONARY-TUBERCULOSIS PATIENTS IN THIS SERIES AT VARIOUS DILUTIONS*	PER CENT POSITIVE OF 340 ADULT PULMONARY-TUBERCULOSIS PATIENTS IN LONDON INVESTIGATION BY P. D'ARCY HART
	per cent	*per cent*
1:10,000	76.4	85
1:1000	97.7	96
1:100	99.4	97.5
1:10	99.6	99
1:1	99.6	99

* Both series are adjusted percentages on the basis that the unfinished cases would react the same way as the others in the same group.

TABLE 3

Data concerning the 22 tuberculous patients who did not react to 1:1,000 dilution

22 PATIENTS		
4	Not tested further	3 expired within 48 hours 1 discharged F.A.A. (old fibroid)
18		
13	were positive 1:100	5 expired within a few weeks 4 F.A.A., chronics, alive 6 months later 2 seniles (68 & 74 yrs.), alive 6 months later 2 M.A.A., alive 6 months later
5		
2	positive 1:10	1 F.A.C., expired in a few days 1 F.A.B., with pneumothorax, expired in 3 months
3		
1	not tested further, expired in 24 hours	
2	negative 1:1, expired in 48 hours	

or guinea-pig inoculation at some time during their stay. Ages varied from 16 to 74 years.

Table 2 shows the percentage positive at the various levels of testing, compared with the adult tuberculous group of 340 pulmonary cases

tested with O. T. by P. D'Arcy Hart (3) in the London investigation of 1929. The percentages are closely parallel.

Vesiculative reactions occurred in 8 patients (all tuberculous). All were relatively mild, causing only very superficial ulceration of the skin over a small area. The patients were from 25 to 49 years old. The duration of disease in these patients was about 1½ yrs., with the exception of one patient whose disease lasted over 20 years. Three of the patients had had artificial pneumothorax. No common reason for the four-plus reaction was noted.

Analysis of patients who failed to react to the 1:1,000 dilution is given in table 3. Of these 22 patients 9 are still alive 6 months later, 8 of whom reacted to the 1:100 dilution. The remaining patients all ex-

TABLE 4

Sensitivity of 926 patients according to sex and age

	AGE														
	16 to 20			20 to 30			30 to 40			40 to 50			50 to 60		
	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total
Number of patients	50	42	92	246	152	398	112	132	244	61	87	148	7	37	44
Per cent negative, 1:10,000	42	22	32	25	23	24	16	13	14	18	20	20	42	30	30
Per cent positive, 1:10,000	58	78	68	75	77	76	84	87	86	82	80	80	58	70	70
Per cent +, 1:1000	86	76	81	66	80	72	59	67	63	70	71	71	50	81	76
Per cent ++, 1:1000	6	21	13	26	13	20	28	23	25	20	19	19	40	9	14
Per cent +++, 1:1000	8	3	6	8	7	8	13	10	12	10	10	10	10	10	10

pired within a very short time. In other words, patients who failed to react to the 1:100 dilution were all moribund, only one surviving more than a few days.

Table 4 shows 926 patients divided according to sex and decade of life. The reaction to 1:10,000 dilution is given as plus or minus, and the 1:1,000 is given as one, two and three plus. The remainder are omitted as of negligible percentage. The sensitivity seems to be lower in the 16- to 30-year age-groups, and rises in the 30- to 50-year groups, falling again in the older patients. This is best seen in the percentage positive to 1:10,000 and in the percentage of three plus 1:1,000.

Seniles: There were 13 patients over 60 years old tested (2 female, 11 male), the oldest 74 years. Diagnoses varied from F.A.A. to F.A.C. (2). Tests with 1:10,000 dilution revealed 7 positive and 6 negative. Two reacted only to the 1:100 dilution.

Table 5 shows data concerning the reactivity of 931 patients according to extent of the lesion. Here there is a definite progressive decrease in skin sensitivity with increasing extent of lesion. This is best seen in examining the percentages of the 1:1,000 dilution. The lower the percentage of one-plus reactions, the higher the percentage of two- and three-plus, and therefore the higher the sensitivity. The percentages in the 1:10,000 dilution are not reliable in demonstrating the quantitative differences in sensitivity because the plus includes all reactions from doubtful to three-plus. The depression of sensitivity in the far-advanced group would be more marked were it not for the fact that many patients with lesions of minimal or moderately advanced extent are classified F.A. because of phrenicectomy, pneumothorax or complications.

TABLE 5

Analysis of reactivity of 931 patients in Min., M.A. and F.A. groups

	MINIMAL			MODERATELY ADVANCED			FAR ADVANCED		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
Number of patients	22	21	43	73	91	164	384	340	724
Per cent negative, 1:10,000	32	28	30	20	22	21	24	24	24
Per cent positive, 1:10,000	68	72	70	80	78	79	76	76	76
Per cent +, 1:1000	60	52	56	61	68	64	68	78	73
Per cent ++, 1:1000	20	24	22	30	23	26	23	17	20
Per cent +++, 1:1000	20	24	22	10	9	9	9	5	7

Symptoms: Table 6 shows the reactivity of patients according to the severity of the symptoms. Here there is a well marked tendency for skin sensitivity to decrease as the symptoms became more intense. The percentages for males and females run parallel.

Duration of disease: Patients whose disease is of less than 6 months' duration show a higher degree of reactivity than the "6 months to 3 years" and the "over 3 years" group. The "over 10 years" group shows a marked depression of sensitivity. Male and female percentages run parallel. There seems to be a progressive decline in sensitivity with prolongation of disease. (Table 7.)

Compression therapy: In 289 patients (table 8) with phrenicoexairesis, pneumothorax or thoracoplasty there is a progressive increase in sensitivity in the order named. Evidently sensitivity rises with increasing degrees of compression of the lesion.

In table 9 the totals of the above groups are combined here for ease of comparison, and a number of smaller groups is included.

Tuberculous enterocolitis, laryngitis and the patients with high temperatures (over 100°F.) show the most marked depression of sensitivity of any group.

TABLE 6

931 patients analyzed according to severity of symptoms

	A			B			C		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
Number of patients	233	254	487	200	160	360	46	38	84
Per cent negative, 1:10,000	21	21	21	25	22	24	39	45	42
Per cent positive, 1:10,000	79	79	79	75	78	76	61	55	58
Per cent +, 1:1000	64	70	67	68	78	73	78	92	85
Per cent ++, 1:1000	26	19	23	23	20	21	10	6	8
Per cent +++, 1:1000	9	11	10	8	2	6	9	2	7

TABLE 7

*Analysis of 934 patients according to duration of disease**

	LESS THAN 6 MONTHS			6 MONTHS TO 3 YEARS			OVER 3 YEARS			OVER 10 YEARS		
	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total
Number of patients	40	44	84	247	245	492	191	167	358	34	34	68
Per cent negative, 1:10,000	22	15	18	24	24	24	22	24	23	15	18	17
Per cent positive, 1:10,000	78	85	82	76	76	76	78	76	77	85	82	83
Per cent +, 1:1000	63	57	60	70	77	73	66	75	70	82	78	80
Per cent ++, 1:1000	25	28	27	22	16	18	24	20	22	15	20	18
Per cent +++, 1:1000	12	15	13	8	7	8	10	5	8	3	2	2

* The "over 3 years" group includes the "over 10 years" group.

Patients (49) who had had a course of sanocrysin had a somewhat lower sensitivity than the average, probably because most were F.A.B. cases. The number is too small for accurate analysis.

The number of patients in each of the groups with associated diseases (diabetes, syphilis, atopic diseases) is too small to render the percentages reliable.

The reactivity of two racial groups is analyzed among the "far-advanced" and "A" groups chosen from 59 Italian and 93 Irish patients.

TABLE 8

Analysis of 289 patients with phrenicoexairesis, pneumothorax and thoracoplasty

	PHRENICOEXAIRESIS			PNEUMOTHORAX			THORACOPLASTY		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
Number of patients	64	46	110	93	69	162	9	8	17
Per cent negative, 1:10,000	30	17	24	18	15	16	22	14	18
Per cent positive, 1:10,000	70	83	76	82	85	84	78	86	82
Per cent +, 1:1000	70	78	74	65	67	66	66	50	58
Per cent ++, 1:1000	24	20	22	25	27	26	11	50	30
Per cent +++, 1:1000	6	2	4	10	6	8	23	0	12

TABLE 9

Total percentages in the various groups

	92 PATIENTS, 16–20 YEARS	398 PATIENTS, 20–30 YEARS	244 PATIENTS, 30–40 YEARS	143 PATIENTS, 40–50 YEARS	44 PATIENTS, 50–60 YEARS	43, MINIMAL	164, MODERATELY ADVANCED	724, FAR ADVANCED	487, "A"	360, "B"	84, "C"	84, < 6 MONTHS	492, 6 MONTHS–3 YEARS	358, > 3 YEARS	68, > 10 YEARS	110, PHRENICS
Per cent negative, 1:10,000	32	23	14	20	30	30	21	24	21	24	42	18	24	23	17	24
Per cent positive, 1:10,000	68	77	86	80	70	70	79	76	79	76	58	82	76	77	83	76
Per cent +, 1:1000	81	80	63	71	76	56	64	73	67	73	85	60	73	70	80	74
Per cent ++, 1:1000	13	13	25	19	14	22	26	20	23	21	8	27	18	22	18	22
Per cent +++, 1:1000	6	7	12	10	10	22	9	7	10	6	7	13	8	8	2	4

	162, PNEUMOTHORAX	17, THORACOPLASTY	87, ENTERITIS	47, LARYNGITIS	46, HIGH TEMPERATURE	49, SANOCRYSIN	8, DIABETES	18, SYPHILIS	13, ATOPIC	24, NEGRO	9, MEXICAN	FROM 59 ITALIAN AND 93 IRISH PATIENTS			
												48, Italian F.A.	85, Irish F.A.	37, Italian "A"	43, Irish "A"
Per cent negative, 1:10,000	16	18	30	26	43	26	13	18	40	33	25	19	18	22	16
Per cent positive, 1:10,000	84	82	70	74	57	74	87	82	60	67	75	71	72	78	84
Per cent +, 1:1000	66	48	84	83	90	78	68	60	69	75	82	85	74	86	72
Per cent ++, 1:1000	26	30	10	14	10	17	25	35	8	16	18	8	22	11	15
Per cent +++, 1:1000	8	12	6	3	0	5	12	5	23	9	0	7	4	3	3

These were selected with the view of contrasting low and high racial or natural (hereditary, not acquired) resistance to tuberculosis. The low-resistance (Irish) group has a somewhat higher skin reactivity than the Italian group.

DISCUSSION

It is evident that all patients with the exception of those on the verge of death react to TPT (Seibert). The present work on 944 adults with pulmonary tuberculosis parallels closely the results of P. D'Arcy Hart with O. T. on 340 adults. There can be no doubt concerning the reliability of this protein fraction for skin-testing. In addition, it offers the advantage of standardization, and an absence of the many extraneous materials present in O. T.

The scattered reports in the literature concerning various types of pulmonary tuberculosis which failed to react were probably due to several omissions in testing: failure to use the intracutaneous (Mantoux) test, failure to use a potent or standardized tuberculin, or failure to follow the usual test dose by tests with stronger concentrations.

The importance of the above considerations lies mainly in the converse of the proposition: namely, if all tuberculous patients react to tuberculin except the moribund, then any nonmoribund patient who fails to react is not tuberculous. The practical application of this conception in actual diagnosis of patients entering a tuberculosis sanatorium has been given more fully in a previous communication (4).

Variations in the size of reactions were studied in an effort to evaluate the factors causing fluctuations in allergy, and in an attempt to analyze the relation of allergy to immunity or resistance.

In the broadest concept, resistance may be viewed as a physicochemical state of the host making him an unfavorable culture-medium for the organism. Allergy is hypersensitivity to tuberculoprotein whereby there is a change in the chemistry of the body, such that minute doses of the protein are capable of injuring or killing the tissues. The question at hand is whether variations in hypersensitivity are associated with variations in resistance, and, if associated, whether either causes the change in the other.

The variations in sensitivity we can measure very accurately. The resistance of the host, however, we can judge only by the end-result, or by a guess based upon the different prognostic factors we see, such as extent of lesion, severity of symptoms, race, age, etc. We have therefore attempted to analyze the variations in sensitivity in regard to each of the prognostic factors in an effort to find significant associated deviations.

The most obvious of these relations is seen in the moribund group of

patients, in whom allergy and resistance are both extremely depressed. The cause for the low sensitivity may, however, reside in the inability of cachetic tissue to react well, or it may be that during overwhelming infection the liberation of tuberculoprotein causes an autogenous desensitization similar to that achieved by repeated injections. Rich (5) favors the latter view.

Examination of the sensitivity in relation to the extent of the lesion shows progressive depression of allergy with greater involvement. It appears quite possible that this depends upon the phenomenon discussed above; namely, that autogenous desensitization is more marked with more extensive lesions.

In the *A*, *B*, and *C* groups, divided according to severity of symptoms, the same effect is apparent. With greater severity of symptoms there is seen a steady depression of sensitivity. The same effect occurs with prolongation of the disease.

Compression of the lung by phrenicoexairesis, artificial pneumothorax and thoracoplasty, seems to be associated with increasing sensitivity in the order named. The more thorough the compression, the greater the skin reaction. This is the opposite of what might be expected of these patients if there were no compression because the phrenicectomy patients are mostly cases of smaller extent and less severe symptoms than the pneumothorax and thoracoplasty patients. This makes it all the more probable that the increase of sensitivity is directly related to the compression of the lung. This again fits in with the theory that the skin reactivity depends upon the amount of tuberculoprotein liberated from the lesion. Apparently the sensitivity may be restored to a higher level when compression procedures cut down the circulation of the tuberculoprotein.

In all of the instances discussed above it has appeared that allergy has a tendency to be depressed in those with a poor prognosis. If we examine, however, the percentages of the Italians in comparison with the Irish we find the opposite to be true. The Irish show a higher sensitivity, although they are generally held to be one of the least resistant races. Furthermore, a number of individual instances were seen of patients with low allergy (+ to 1:100 dilution) who were doing well clinically, and *vice versa*.

It is evident, then, that the variations in allergy seen in this study do not have the same relation in all instances to the variations in resistance. In some the two take parallel directions; in others, divergent directions.

Thus it can hardly be considered that allergy is a major cause of variations in resistance. It appears rather that the main variations in allergy can be explained as results of the liberation of tuberculoprotein, which in turn depends mainly upon a failure of resistance. Thus, with a well-walled-off lesion, allergy would remain high, but, with failure of resistance accompanied either by extension of the lesion or by more activity with more marked symptoms, progressive depression of allergy would occur.

Variations in allergy might by this concept be considered a by-product of resistance.

The ideas expressed above apply only to resistance-allergy relations after allergy has once been established, and have no direct bearing upon the question of the relative resistance before and after allergy appears. Nor is any explanation offered here for the complete suppression of skin sensitivity which is said to occur in some patients who have had well-healed lesions for many years. This would depend upon an understanding of the mechanism which keeps up or renews skin sensitization. Variations in the latter mechanism may possibly be another cause for fluctuations in allergy.

The level of sensitivity may perhaps be looked upon as representing a dynamic value depending upon sensitization on the one hand and desensitization by liberation of tuberculoprotein on the other. A more active lesion favors the latter, while compression favors the former process.

The generalizations made in this study are founded upon statistical evidence which depends for accuracy upon the volume of observations. There is no doubt that a considerable number of individual exceptions occur.

SUMMARY

Tuberculous patients in this series all reacted to TPT (Seibert) intracutaneously, with the exception of a few on the verge of death: 97.7 per cent reacted to the 1:1,000 dilution. Two-thirds of those who did not react to this dilution were moribund. About one-third (all of whom reacted to the 1:100 dilution) are still alive 6 months later.

Quantitative studies indicate that skin sensitivity is progressively depressed with advancement of the lesion, with increasing duration of disease, and with increasing severity of symptoms. Skin sensitivity is progressively increased with increasing degrees of lung compression. The sensitivity of a number of other groups was studied. No evidence

was found that allergy influences immunity. It seems rather that immunity indirectly influences allergy through the liberation of antigen.

CONCLUSIONS

1. TPT (Seibert) is a reliable form of tuberculin for intracutaneous testing.

2. A series of 944 tuberculous adults was tested, all of whom gave positive reactions, with the exception of a few who expired within several days.

3. Skin sensitivity diminishes as the lesion becomes more extensive, as the symptoms become more intense and with duration of disease.

4. Skin sensitivity increases with artificial compression of the lesion.

5. The major clinical fluctuations in allergy are probably dependent upon the ease of liberation of tuberculoprotein from the lesion.

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THE HEALING OF TUBERCULOUS CAVITIES (CONTINUED)

A Study of Cavities in a Middle-Age Group[1,2]

LOUIS H. FALES AND E. A. BEAUDET

It is agreed by all phthisiotherapists that tuberculous cavities should be eliminated in the patient. One with a cavity is constantly exposed to dangerous complications, such as laryngeal tuberculosis, tuberculosis of the intestines, haemorrhage, exudative extensions and degeneration of the viscera.

As to how we shall proceed in the healing of cavities, there is, however, a considerable difference of opinion. To bring about a discussion of this question is one of the purposes of this paper.

The opinions of clinicians have unfortunately been greatly influenced by Graeff's statement made at Bad Elster in 1921, that the tuberculous cavity was the death-sentence of the bearer. That spectacular pronouncement has been quoted and requoted, and has left an unduly deep impression on the medical profession. We have always thought that Graeff's statement was far from the truth, and at present it is not at all tenable, as favorable after favorable results have followed the treatment of cavities by rest and improving surgery of the chest.

In 1930 the authors published an article, *The Healing of Tuberculous Cavities*. It was the result of a statistical study of a series of cavity cases, the object being to determine what percentage of cavities healed by strict rest in bed.

The conclusions were, briefly, that a large percentage of cavities healed by strict bed-rest, and that healing depended greatly on the size of the cavities and the amount of pulmonary involvement. Of cavities 2.5 cm. in diameter or less, 66 per cent healed, while, of the larger cavities, 23 per cent healed.

When the amount of pulmonary involvement was minimal or moderate, 62 per cent healed, while, when it was extensive, 30 per cent healed.

Although we had tried to make the study as accurate as possible, the findings in our first paper brought forth considerable criticism, mainly

[1] From the Veterans Administration, Livermore, California.

[2] Presented before the Laennec Society, San Francisco, California, May 5, 1933.

from those who advocated early thoracic surgery in all cavity cases. The point at issue was that the percentage of cavities that healed by rest seemed inordinately high.

On account of this doubt registered in some quarters, it was decided to observe another series of cavities in order to prove or disprove the previous conclusions.

Our second series was studied from a somewhat different aspect. In the first series, as stated above, the healing of cavities was studied more in relation to their size and the amount of pulmonary involvement. In the present series we have studied the healing of cavities in relation to their age, the type of lesion present, and the progress of the lesion.

There were available for the present study at the hospital 296 tuberculosis cases, a few arrested or on the verge of arrest, others active minimal, moderately advanced and far advanced.

A survey of these cases showed 114 cavity cases and 122 cavities either open or healed.

Twenty-six cases were discarded because they had not been in the hospital one year;[3] three on account of having undergone thoracic surgery less than one year after entrance to the hospital; two on account of the development of pleurisy with effusion which obstructed the view of the lung-field; and one complicated by rather severe extrapulmonary complications. There were left 90 cavities for consideration.

The age of this group of cavity cases should be emphasized. It is to be borne in mind that all of our arguments and conclusions which follow were based on the results attained in the treatment of a middle-aged group and perhaps would have been somewhat modified had we treated adolescents or a series in the twenties.

One was 29 years of age. Seventy six, or 92.7 per cent, were between 31 and 45. The average age was 39 years and two months. All were World War Veterans except one, who was a Spanish American Veteran.

There have been several classifications of cavities. The most generally accepted is that by Pinner (2). The adoption of this classification was considered, but as we desired especially to study the healing of cavities according to their age, it was necessary that we choose a classification with that point in mind.

[3] Less than one year was considered hardly a fair trial for the healing of cavities by rest. An unhealed cavity case, therefore, was not added to our series until a year's period of observation had been reached.

In our study of cavities it was noted that the different types of cavities corresponded quite uniformly to the pathological changes present. It was therefore decided to classify cavities according to the type of lesion of which they were a part. As a basis for such a classification, we adopted the well known pathological entities: exudative, productive and fibrotic.

It will be necessary here to digress, while we give a short description of the development and progress of these lesions, so that it may be better understood why we decided on this classification.

On account of lack of space we discuss only the roentgenographic description of the development of tuberculous lung pathology. This description is based on Assman's and Redeker's newer concept that secondary (Ranke) or adult tuberculosis usually begins as an exudative infiltrate in some portion of the lung below the clavicle and that the productive and fibrotic types of tuberculosis, often apical, are, as a rule, late clinical manifestations of the infection.

The exudative lesion appears roentgenographically in any part of the lung, but usually below the clavicle as a soft, fairly circular or irregular homogeneous area of varying density, and with poorly defined borders.

The productive lesion, a later development, is characterized roentgenographically by irregular clover-leaf shaped shadows of medium density with moderately well-defined margins. These shadows give the film a diffuse mottled appearance in the upper lung field: below, the areas are smaller and more scattered.

The lesion finally merges into the fibrotic type and appears as discrete densities, band-like and linear markings all with well-defined borders, shapely outlined stellate shadows; diffuse shadows of irregular density, all with clear-cut margins; deformities as displacement of the heart, trachea, mediastinum and interlobar fissures.

A lesion may be mainly productive or fibrotic, but an exudative cavity may be present in another portion of the lung, secondary to, or a part of, a recent infiltrate. As tuberculous processes undergo a gradual progression from one type to another, in the same manner the tuberculous cavity, an integral part of the lesion, shows a progressive development, its characteristics depending on the stage or age of the process.

We have, therefore, classified cavities into exudative, productive and fibrotic, corresponding to the type of tuberculosis of which they are a part.

The exudative cavity first develops roentgenographically as an area of diminished density with no surrounding wall in a homogeneous area of density. Its outline may be first irregular, but, as liquefaction and

expulsion continue, a circular line of demarcation appears, to mark out the borders of the developing cavity. As resorption of the infiltrate proceeds, the area of diminished density may appear to have a fairly

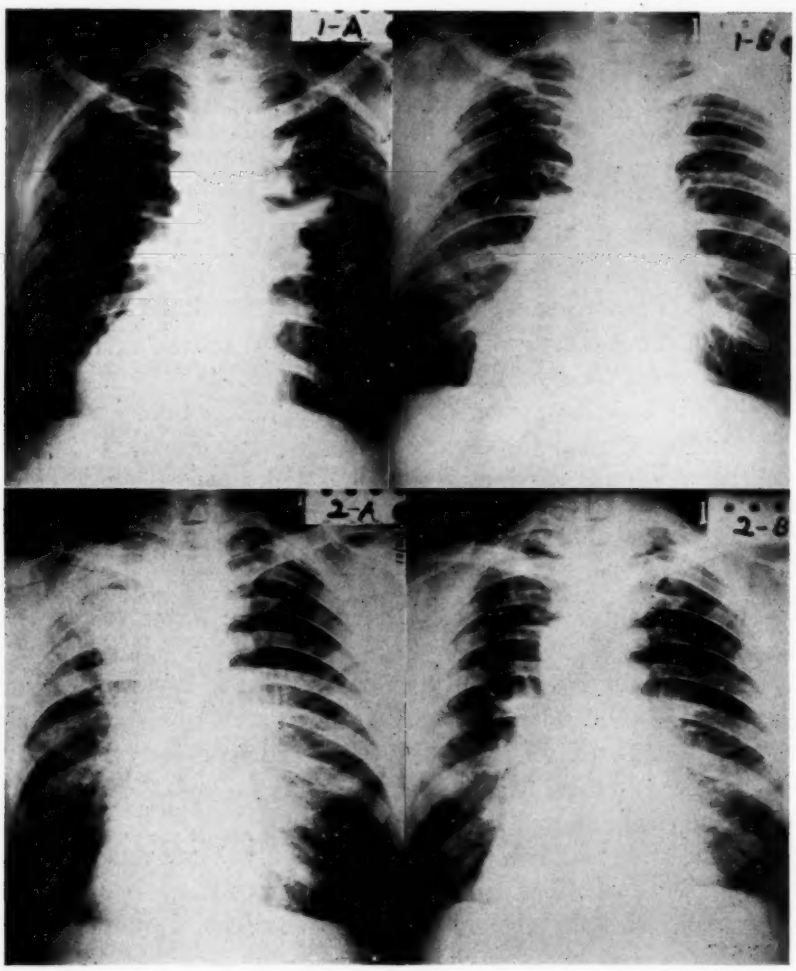

FIG. 1 FIG. 2

FIG. 3 FIG. 4

FIG. 1. Case 1A. A large exudative cavity in right lung. The cavity wall is moderately thick and has a soft, fuzzy appearance. Some exudate still remains below the cavity.

FIG. 2. Case 1B. The cavity has entirely healed, leaving a moderate-sized scar.

FIG. 3. Case 2A. Films taken July 13, 1931. A very young exudative cavity appearing in a moderate-sized infiltrate; apex, left lung. The cavity wall has not yet developed. Only a thin line of demarcation can be seen.

FIG. 4. Case 2B. Films taken October 23, 1931. Within about three months there has been resorption of the exudate and the cavity has entirely healed.

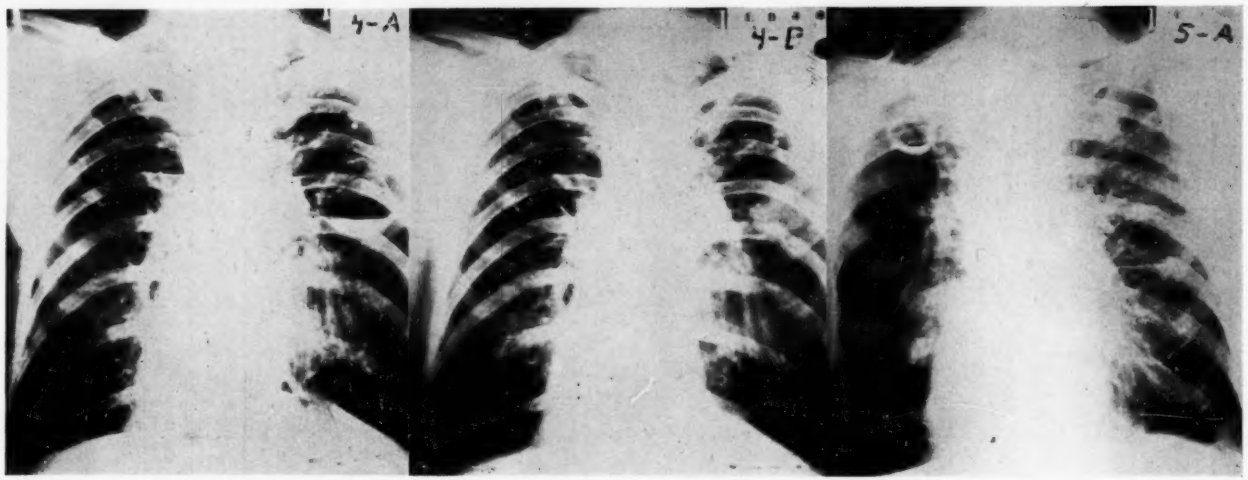

FIG. 5 FIG. 6 FIG. 7

FIG. 5. Case 4A. Films taken February 23, 1932. A large productive cavity, right lung. The wall is somewhat irregular in outline, is of medium thickness, and has a moderately hard appearance. A fluid level is also present.

FIG. 6. Case 4B. Films taken May 17, 1932. The cavity has healed, having been replaced by a fairly large fibrotic scar.

FIG. 7. Case 5A. A moderate-sized fibrotic cavity, left upper lobe. The cavity-wall is irregular in outline, appears hard and thick, and is apparently densely fibrotic. After eighteen months' strict bed-rest, the cavity had not appreciably changed.

thick, soft wall, due, no doubt, to remains of the infiltrate. Further resorption continuing, all exudate may disappear around the cavity, and,

TABLE 1

Classification of cavities

CLASSIFICATION BY PINNER		CLASSIFICATION USED BY AUTHORS IN STUDY OF CAVITIES	
Types of cavities	Roentgenological description of types	Types of cavities	Roentgenological description of types
1. Small multiple cavities	Small, multiple cavities in densely infiltrated parenchyma, the roentgenological appearance of which is frequently described as "moth-eaten areas"	1. Exudative cavity	First develops as an area of diminished density with no surrounding wall in a soft homogeneous area of density. Its outline may be first irregular, but, as liquefaction and expulsion continue, a circular line of demarcation appears, marking out the borders of the developing cavity. Later a definite soft-appearing wall develops, often somewhat thick due to the remains of the infiltrate. As the exudate continues to disappear the cavity finally appears as a circular shadow with a thin soft wall
2. Round or slightly oval cavities	Sharply defined, almost completely round or slightly oval cavities, either with heavy perifocal infiltration or with thin, clearly defined borders	2. Productive cavity	Appears usually as a circular or oval area of diminished density surrounded by a rather thin and moderately soft wall. All exudate has disappeared. As the productive cavity becomes older the walls may become thicker, harder and with more sharply defined borders
5. Irregular-shaped cavities	Irregularly shaped cavities with dense walls, often of grotesque shape with marked irregularities in the walls	3. Fibrotic cavity	May be circular in outline but is often deformed, contracted or shrunken. The walls are usually thick and appear hard and dense with clear-cut margins

as fibrous tissue develops in the line of demarcation, a circular shadow with a thin soft wall appears.

The productive cavity: As there is a gradual progression from the exuda-

tive to the productive lesion, so also is there a gradual progression from the exudative to the productive cavity. Border-line cavities may be found which might be classified either as exudative or productive. Often the determining factor is that in productive cavities all exudate has disappeared. Radiographically the productive cavity appears as a circular or oval area of diminished density surrounded by a rather thin and moderately soft wall. As the productive cavity becomes older the walls may become thicker, harder, and with more sharply defined borders.

The fibrotic cavity, a still later development, appears roentgenographically as a more or less circular or irregular area of diminished density surrounded by walls which are usually thick, and seem dense and hard.

As previously stated, the above classification was adopted for our study rather than the well-known classification by Pinner, because the former separated the cavities more strictly as to their age. These classifications are compared in table 1.

It was considered that Pinner's no. 2, *Round and Slightly Oval Cavities*, covered too much ground for our purpose. The types that would have been included in Pinner's no. 2 by our classification were divided into two types, namely, no. 1, *Exudative*, and no. 2, *Productive*. This gave us the opportunity to determine statistically how many of the very young cavities healed as compared with the older types. This could not have been done if we had used Pinner's classification. Pinner's no. 1, *Small Multiple Cavities*, an exudative type, was included in our no. 1. In the present series there were very few cavities of that variety.

Analysis of the cavity study:[4] This appears in table 2. Of the 90 cavities of the series, 29 were classified as exudative, 49 as productive, and 12 as fibrotic. The cavities varied in size, from 1.5 to from 6 to 8 cm. in diameter. Many that healed were large, one being 4.5 x 8 cm. As to the shape of the exudative cavities, 93 per cent were round or oval; of the productive, 80 per cent; and of the fibrotic, 50 per cent.

The walls of the cavities were classified under three heads: (1) absence of cavity walls, (2) thin walls and (3) thick walls. Approximately 24 per cent of the exudative cavities had no walls, or an almost indiscernible thin line of demarcation; 55 per cent had thin walls and 21 per cent thick walls. Of the productive cavities 60 per cent had thick walls and the

[4] Nearly all annular shadows and well-circumscribed areas of diminished density were considered cavities, but only after a careful study by comparative stereoroentgenograms. A cavity was considered healed when the annular shadow or diminished opacity had entirely disappeared or had been replaced by a comparatively hard, irregular density.

TABLE 2

CLASSIFICATION	NUMBER OF CAVITIES CONSIDERED	TYPE OF CAVITIES					CHANGES IN THE CAVITIES																		TIME OF HEALING					
		Shape		Walls			Healed					Smaller				Larger				No change											
									Course of lesion					Course of lesion				Course of lesion					Course of lesion							
		Round	Irregular	No walls	Thin	Thick	Number	Per cent	Retrogressive	Progressive	Stationary	Number	Per cent	Retrogressive	Progressive	Stationary	Number	Per cent	Retrogressive	Progressive	Stationary	Number	Per cent	Retrogressive	Progressive	Stationary	Six months	Per cent	Six months to twelve months	Per cent	Over one year	Per cent
Exudative.....	29	27	2	7	16	6	19	66	19	0	0	6	20	6	0	0	4	14	3	1	0	0	0	0	0	0	11	58	7	37	1	5
Productive.....	49	39	10	0	20	29	21	43	21	0	0	10	20	8	2	0	11	23	1	9	1	7	14	3	4	0	3	14	11	52	7	34
Fibrotic.....	12	6	6	0	2	10	2	17	2	0	0	3	25	1	0	2	2	17	0	0	2	5	41	0	0	5	1	50	0	0	1	50
Total.....	90	72	18	7	38	45	42	46.6	42	0	0	19	21.1	15	2	2	17	18	4	10	3	12	14.3	3	4	5	15	36	18	43	9	21

remainder thin walls. Eighty-three per cent of the fibrotic cavities were classified as having thick walls. Since there is considerable difference of opinion as to what constitutes a thin- or thick-walled cavity, others might not agree with the above classification.

The percentages of the cavities that healed seemed very significant. It was found that, of the 29 exudative cavities, 19 healed, or 66 per cent; of the 49 productive cavities, 21 healed, or 43 per cent; but of the 12 fibrotic cavities, only two healed, or 17 per cent.

Table 2 also shows that the healing of cavities ran parallel to the retrogression of the accompanying lesions.

The length of time required for the healing of cavities by strict bed-rest also appears in table 2.

Of the 19 exudative cavities that healed, 11, or 58 per cent, healed in six months; 7, or 37 per cent, in from six to twelve months, a total of 18, or 95 per cent, within one year.

Of the 21 productive cavities that healed, 3, or 14 per cent, healed within six months; 11, or 52 per cent, in from six to twelve months,—a total of 14, or 66 per cent, within one year.

Of the two fibrotic cavities that healed, only one, or 50 per cent, healed within one year.

DISCUSSION

It seems to us that the healing by rest of 46.6 per cent of all cavities,—of 66 per cent of the exudative and 43 per cent of the productive, to say nothing of the large number which became smaller,—is a most important therapeutic issue. It makes us wonder why some do not seem to appreciate the value of rest treatment, and whether some are not resorting too soon to surgical compression.

It is well to state here that in our series there were five who, on account of their extensive involvement, as indicated clinically by high fever, etc., were considered hopeless. Two of these have already died. We should, perhaps, have discarded these cases from our list, but they were retained.

It should be emphasized that while 66 per cent of the exudative and 43 per cent of the productive cavities healed, only 17 per cent of the fibrotic cavities healed. The above suggests that we distinguish between the young and old cavities and that the prognosis and treatment for each type should be differentiated. It also brings into question the judgment of those who advocate the compression of all cavities without regard to type.

It has been stated that although cavities may close by rest, a true healing does not take place, and a large percentage reopens. After observing cavities in our series for an average of one year and four months, two reopened. These accidents occurred after one patient had persisted in frequent visits to his home, and after the other had gone on a four days' leave and returned in a half-intoxicated condition.

Personally, we have never seen a cavity, once closed, reopen, when the patient had been kept sufficiently long on strict bed-rest.

When shall we employ rest alone and when shall we complement rest by surgical compression in the treatment of cavities?

Those who advocate immediate or early surgical intervention in pulmonary cavities base their opinions largely on the following reasons:

1: That tuberculous lesions treated by rest are nearly always progressive and that cavities almost never heal unless rest is supplemented by thoracic surgery.
2: That the walls of cavities, as they grow older, rapidly become thicker and more fibrotic, making them more difficult to collapse and heal, even by mechanical means.
3: That the early application of surgical intervention will hasten the healing of cavities,—an important economic factor, allowing the patient an early return to normal life.

Although there is a little truth in the above premises, there is also a great deal which is erroneous, as we will try to bring out in this discussion.

In regard to item *1*, we believe it has been demonstrated that extremely satisfactory results may be attained by well-supervised rest in bed, in the treatment of tuberculosis with cavitation as well as in tuberculosis in general.

As to item *2*, it is true that the walls of cavities as they grow older will become thicker. This is especially the case in patients who are allowed considerable exercise. In most patients who are kept on strict bed-rest, it is quite different. The cavity-walls increase in thickness very slowly, and we have observed in the healing of some cavities, especially the acute or exudative, that the walls often become thinner and almost disappear as the cavity is about to heal. In fact the majority of the exudative cavities will have healed before the cavity-walls have had a chance to become dense and fibrotic.

In regard to item *3*, can we economize in time by early surgical interference in the treatment of cavities? It is true that in many of the rapidly disintegrating types and in those that already have thick fibrous

walls, there should be no delay. In the more simple exudative types and in many of the productive types, however, a saving of time by early compression is doubtful. After compression a patient may manage with less rest and may take part in certain activities, but does actual healing occur much sooner? It seems sometimes that the false security engendered by the surgical procedure influences the patient to be so active that healing is retarded. Pottenger (6) recently expressed the view that no matter what method is used in the treatment of cavities, it must be borne in mind that it takes a long time to bring about a permanent healing; that cavities subjected to surgical collapse still must heal like other tissues that are infected.

The fact that some are advocating that pneumothorax be continued a greater length of time,—from three to five years,—suggests two things: first, that a too large percentage of pneumothoraces have been found insufficiently healed when the lung has been allowed to expand; and, second, that it may take compressed lung tissue even a longer time to heal than uncompressed lung tissue.

Chest surgery is no doubt the most important development in the treatment of pulmonary tuberculosis during the last fifteen years, and, as time goes on, it is bound to improve in effectiveness; but, at this writing, we do not believe that we are ready to have it overshadow rest in the treatment of all types of cavities. For example, it would have been little short of malpractice to have instituted pneumothorax treatment in any of the 66 per cent of the exudative cavities that healed. Such patients would have been burdened by repeated refills and their dangers, extending over years. As it is, 50 per cent of those having the exudative cavities have reached the stage of arrest, 19 per cent are near arrest,[5] 23 per cent are improving, and 6 per cent have been lost sight of.

Even of the cases having productive cavities that healed, 33 per cent have reached the stage of arrest, 28 per cent are on the verge of arrest, 22 per cent are improving, 5 per cent are worse and 11 per cent have been lost sight of.

What logical conclusion may we draw from the above discussion?

We have tried to give the facts as we find them in regard to the healing of cavities, and do not wish to be too arbitrary in our conclusions. As a general rule, which has its exceptions, it would seem that practically all exudative cavities of the middle-age group should be treated by strict

[5] By "arrest" we mean an anatomical, not a symptomatic, arrest.

rest in bed, such rest to continue for at least one year without pulmonary compression, provided the lesion continues to retrogress and the cavity to become smaller; that a large percentage of the productive cavities should also be treated by strict bed-rest (continuance of rest depending on the results attained), and the selection of the cavities for rest depending greatly on the location of the cavity, its proximity to the pleura, the character of the cavity-walls, and the progression or retrogression of the lesion; and, finally, that all fibrotic cavities should be recommended for surgical intervention at once.

Although the above may serve as a general guide, it must be realized that each cavity case is a problem in itself and must be treated individually, depending on many factors, such as, for example, general condition of the patient, complications, mental attitude, etc.

CONCLUSIONS

1. In the treatment of pulmonary tuberculosis, one of the most important problems is the elimination of cavities.

2. There is considerable difference of opinion as to how to proceed in the treatment of cavities. Some advocate the early immediate compression of all cavities, while others believe that rest in bed should be the main reliance, especially in their early treatment.

3. In order to facilitate this study, cavities were classified as *exudative, productive and fibrotic.*

4. The healing of cavities usually accompanies retrogression of the lesion. When the lesion is progressing, the cavity as a rule does not heal.

5. It would appear that we have confirmed our previous findings that a large percentage of cavities, especially of the middle-aged group, will heal by strict bed-rest. Our conclusions are based on the study of 237 cavities, 147 in our first series and 90 in our present series.

6. In our present series it was demonstrated that the young or exudative cavities responded most favorably to bed-rest (66 per cent healed); the moderately old or productive cavities less favorably (43 per cent healed); and the old or fibrotic cavities unfavorably (only 17 per cent healed).

7. The logical conclusions to be drawn from *5* and *6* above are:

a. That young cavities should be treated quite differently from the older types.

b. That at the beginning nearly all exudative cavities should be treated at once by strict bed-rest; that a large percentage of productive

cavities should also be treated by strict bed-rest; but that practically all fibrotic cavities be recommended for surgical procedure at once.

c. That although chest surgery is one of the most important developments in the treatment of pulmonary tuberculosis in recent years and is bound to improve in effectiveness, we are not ready to have it overshadow rest in the treatment of all types of cavities.

8. In the treatment of tuberculous cavities by bed-rest, it is very necessary that patients be under frequent competent roentgenographical control, so that increase of the size of the cavity or the development of new areas of infiltration may be detected early, a warning to modify our treatment, always having in mind surgical compression, to be resorted to when deemed expedient.

9. Rest treatment means to some, rest in bed eight hours at night, one or two hours' rest in the morning and one or two in the afternoon, the patient being left to his own devices the remainder of the time. To others it means absolute control and supervision during the entire twenty-four hours, with rest ranging from 22 to 24 hours in bed, and absolute rest where response is slow to the lesser amounts. Only those who adopt the latter regimen can expect consistent results from rest in the healing of cavities.

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SIMULTANEOUS BILATERAL SPONTANEOUS PNEUMOTHORAX

A Review of the Literature and Report of a Recurrent Case Due to Congenital Cysts of the Lung[1,2]

WALDO R. OECHSLI AND SETH H. MILES

Simultaneous spontaneous collapse of both lungs has been known as a clinical entity for over two hundred years. Boerhaave, in 1724, described a case due to rupture of the oesophagus from vomiting. The clinical features of the condition were accurately described by Laennec in 1816, in his *Traite de l'auscultation médiate.* In spite of this early recognition, it has been considered an extremely rare condition. In the last quarter-century, however, coincident with practical roentgen-ray diagnosis of chest pathological processes, an increasing number of cases is being reported.

TERMINOLOGY

While the classification of pneumothorax and the designation of the various types is, in the main, sufficiently well defined, certain terms are used in such a varying sense by different writers as to be quite confusing. The term *spontaneous*, defined by Dorland as "occurring without external influence," is sometimes limited to apply only to "idiopathic" cases, but it seems reasonable that all instances of pneumothorax, except traumatic and induced, should be designated as "spontaneous," whether due to (1) some demonstrable pathological change in the lung or pleura, which actually or presumably causes perforation of the latter; (2) some cause which cannot be demonstrated; or (3) infection with gas-producing organisms. The term "idiopathic," defined as "self-originated," and implying a collapse in a perfectly normal individual without the intervention of pathological change, is not altogether in accord with recent ideas of the pathogenesis of spontaneous pneumothorax but general usage justifies its use to indicate collapse without demonstrable cause.

[1] Presented, in part, before the Trudeau Society of Los Angeles, California, January 27, 1931.

[2] An earlier report with 69 collected cases appears in Tubercle, June, 1934, xv, 402.

In bilateral pneumothorax, Olbrechts (1) stipulates that simultaneous, bilateral collapse refers to those instances in which the two lungs collapse at the same instant, or the second lung collapses before the first lung collapsed has reëxpanded. This is in contradistinction to successive collapse.

REVIEW OF THE LITERATURE

In collecting this series of cases, we have confined consideration to cases of simultaneous, bilateral, spontaneous pneumothorax, excluding traumatic cases, successive cases, those complicating induced pneumothorax and, of course, bilateral induced pneumothorax. Boerhaave's case, mentioned above, is not included, since it might be considered in a sense traumatic. Over 20 cases, regarding which little or no data are available, have been omitted. Two cases, reported by Grashey (2) and Bourne (3), are referred to by several authors as cases of bilateral collapse. The case reports indicate a complete, unilateral collapse, in each instance. After these exclusions, there remain 76 cases which answer the above description.

INCIDENCE

During the period from 1814, when Laennec observed the first of two cases, to 1900, when the roentgen-ray began to be used in diagnosis of chest conditions, only 21 cases were reported. Since 1900, 55 cases have been found (*ref.* (4) to (63)). Granting that more medical literature on all subjects has been published in late years, it is probable that many cases of double pneumothorax were not diagnosed in the preroentgen era, as during that period there are recorded very few cases of emphysema and no idiopathic cases, both conditions in which the X-ray is invaluable in diagnosis.

AGE

The incidence in the various age-groups for the series is largely dependent on the character of the underlying pathological process. Thus, tuberculous cases fall almost all together in the period from 15 to 35 years. The trend in idiopathic cases is toward the younger age-groups. In the emphysematous group the more elderly predominate.

SEX

The sex factor is of some interest in that 80 of the patients are of the male sex, a disparity often noted in unilateral spontaneous pneumothorax. Figures from the tables of 11 authors show an average of 78 per cent of

909 patients with unilateral spontaneous collapse to be males. Why this should be is not clear. Scott (64) considers it as accidental. Norris and Landis ascribe it to the fact that figures on spontaneous pneumothorax are secured from hospital records, male patients predominating in hospitals. Lord attributes the difference to the more strenuous and exposed life of the male. Pneumonoconiosis and emphysema, occurring more frequently in men, add certainly to the disparity, as do the above-mentioned facts. We feel, however, that the real cause for the disparity is yet to be revealed.

AETIOLOGY

Pulmonary tuberculosis stands at the head of the list as the aetiological factor in bilateral as in unilateral collapse (table 1). Slightly

TABLE 1

Aetiology and mortality in bilateral spontaneous pneumothorax

UNDERLYING PATHOLOGICAL CHANGE	NUMBER	PER CENT TOTAL	RECOVERED	DIED	PER CENT MORTALITY
Pulmonary tuberculosis	39	51	6	33	85
Idiopathic	17	21	13	4	23
Emphysema	10	13	4	6	60
Pneumonoconiosis	3	4	2	1	33
Bronchopneumonia	2	3	0	2	100
Congenital cyst	2	3	1	1	50
Malignant tumor	2	3	0	2	100
Bronchiectasis	1	1	0	1	100
Interstitial fibrosis	1	1	1	0	0
Total	77	100	27	50	65

over half of the patients are tuberculous. In Biach's much-quoted series of 918 cases of unilateral collapse, 715 were tuberculous. Weil found 46 out of 55 tuberculous, Drasche 198 out of 230, and Mosheim 43 out of 50. Totalling these figures, we find 1,002 tuberculous cases out of 1,253, or 80 per cent. The difference between this figure and the 51 per cent of our series of bilateral cases is probably not accidental. Tuberculosis is prone to involve one lung to a greater extent than the other as it advances. On the other hand, pathological changes which involve both lungs equally and are capable of causing pulmonary collapse should cause a relatively higher percentage of double collapse. This we find to be the case in emphysema, which accounts for 13 per cent in our series as compared

with less than one per cent in unilateral cases (Biach). For idiopathic cases we find no suitable figures for comparison. No cases of gangrene, lung abscess or empyema were encountered. In Ebert's case of bilateral empyema, often cited as bilateral, spontaneous pneumothorax, there is no evidence that pneumothorax was not incidental to the surgical drainage instituted.

The immediate cause of collapse in the tuberculous cases was perforation of the visceral pleura by cavities. In emphysema, rupture of dilated air-vesicles occurred. In a few cases, more than one condition existed—as a ruptured cavity in one lung and air-vesicle or bleb in the other. In Buzin's case, in addition to the tuberculous involvement which caused collapse in both lungs, there was a carcinoma in one lung with a distal bronchiectasis. In the cases of bronchiectasis, bronchopneumonia and malignant tumor, perforation of the pleura resulted from necrosis of pathological lung tissue. In two of the 4 fatal idiopathic cases, necropsy failed to show the cause. Many possible causes of collapse in this latter class of cases have been advanced, such as small subpleural tuberculous foci, localized emphysematous blebs, tearing of the lung tissue at the site of adhesions on strenuous or unusual exertion, etc. Tuberculosis can sometimes be ruled out by means of tuberculin. The patient observed by Smith and Bosworth was negative to tuberculin intracutaneously in the stronger dilutions and showed no constitutional reactions and was still negative on physical and roentgenological examination.

PROGNOSIS

The outlook for patients with bilateral spontaneous pneumothorax has always been considered exceedingly gloomy. In fact, earlier it was thought to be incompatible with life. We were somewhat surprised, therefore, to find that as many as 35 per cent of these patients recovered from the double collapse (table 1), though many of these later succumbed to the underlying pathological involvement after reëxpansion. Much variation, however, is noted in the different groups. The figures for tuberculosis almost justify the application to bilateral pneumothorax of the pronouncement of Lebert who, in speaking of unilateral pneumothorax in the tuberculous, said he "doubted the diagnosis of any reported recovery." Of the 39 tuberculous patients, 33, or 85 per cent, died as a result of the double collapse. In sharp contrast to these results, the collapse was fatal in less than one-fourth of the idiopathic cases. Over half of the emphysematous patients died.

METHOD OF DEVELOPMENT OF BILATERAL COLLAPSE

The question of whether the bilateral collapse results from a separate perforation of the pleura on each side or from a single perforation in one lung accompanied by a defect in the mediastinum, allowing air to pass through to the opposite pleural cavity, was discussed by LeWald. Out of the 50 fatal cases, this can be answered definitely in 31 cases which came to necropsy. Frantzel's case was the only one in which double collapse did not result from perforation in both lungs. In this patient, the anterior mediastinum was converted into a caseous mass by the tuberculous process, with many points of communication. A rupture of a cavity in the right lung caused collapse of both lungs. One of Emerson's collected cases is somewhat similar, in that a right upper-lobe cavity ruptured mesially through the mediastinum, causing collapse of the left lung. The right lung did not collapse because of extensive adhesions around the site of perforation. Walsh (65) McCallum (66) and Ioganson and Prozorov (67) each report a case in which bilateral collapse followed the induction of unilateral pneumothorax. In one case, the mediastinum was ruptured, apparently by pressure. In the two others, a patency of the mediastinum was suspected, though not proved. The possibility of a spontaneous pneumothorax in the contralateral lung must be considered. At any rate, patency of the mediastinum must be exceptionally rare or it would be encountered more often in induced pneumothorax.

RECURRENCE

Recurrent spontaneous pneumothorax is much more common among the nontuberculous, probably because it is less fatal in these cases. All of the 7 cases in the series in which there was recurrence were nontuberculous. In most of these there was simply a history of symptoms suggesting a previous collapse. In several, successive collapses took place under observation of the physician, but they occurred before the lungs had entirely expanded. Our case is the only one encountered in which more than one double collapse, with complete reëxpansion in the meantime, was demonstrated by X-ray.

Case Report

L. C., messenger boy, age 22. During school-years, he took part in competitive athletics and was not conscious of any physical handicap, although other members of the family state that he was never as strong as other boys. In 1918, he had a mild influenza, with slight fever and cough but no expectoration.

In January, 1927, he again became ill with influenza. He coughed considerably and for several days raised some clear, mucoid sputum which was negative for tubercle bacilli. There was a history of diabetes insipidus.

Present Illness: During the evening of November 2, 1928, while sitting quietly, listening to the radio, he noticed a fairly sharp pain in the right side of his chest. Dyspnoea was not noticed. The second night, the pain became worse and considerable dyspnoea was present; in fact, he could rest only when propped up in a sitting position. The next morning, he consulted a physician whose diagnosis was pleurisy. The patient applied a plaster over his right axilla. The dyspnoea persisted and he continued sleeping at night propped up in a chair for two weeks. He then returned to his physician who discovered a partial collapse of the right lung and sent him at once to a hospital. During the following night, he had pain in his left side, associated with increased dyspnoea. X-ray examination next day disclosed a partial collapse of both lungs (figure 1). A more complete collapse was prevented by fine adhesions. Very little change was noted during the next few weeks, and he was admitted to the Olive View Sanatorium as a tuberculosis patient, January 23, 1929.

Examination at that time revealed a stockily built young man. Nutrition good, with considerable fat over the body. The fingers were considerably clubbed and somewhat cyanotic; the chest short and deep; breath-sounds distant over both lungs, particularly at the bases; the percussion note rather tympanitic; and numerous coarse râles heard over the bases. The temperature ranged from 97.0° to 99.0°F., the pulse from 70 to 100 and respirations from 24 to 30. Blood-pressure, 88/68; blood-sedimentation time (Linzenmeier) 69 minutes; white blood cells, 12,400; haemoglobin 79 per cent; Wassermann negative. The intracutaneous tuberculin test was slightly positive to 0.1 mgm. O.T.; the urine pale, of low specific gravity, and negative for albumin or sugar.

X-ray examination showed both lungs nearly expanded and, as the symptoms were not urgent, air was not aspirated. Within three months all the air had been absorbed. The patient did very little during the next year, fearing a return of the pneumothorax.

During the night of June 2, 1930, he was awakened by a severe, sharp pain in the left chest. Moderate dyspnoea was manifest at this time. He again entered a hospital, and X-ray revealed another bilateral collapse of the lungs. There was more collapse this time than previously. He was carefully watched and, as expansion commenced very shortly, no air was aspirated. In six weeks time, reëxpansion was complete. In November, 1930, the vital capacity was 2000 cc., or 48 per cent of normal. At this time, he was conscious of only slight dyspnoea on such exertion as climbing stairs.

Nine months later, in response to our inquiry as to his condition, he came to see us. About a week earlier he had had an acute respiratory infection, start-

FIG. 1

FIG. 2

FIG. 1. Partial collapse of both lungs. After reëxpansion, the patient suffered another bilateral collapse, and still later a unilateral collapse.

FIG. 2. After complete reëxpansion, iodized oil was instilled into the lungs. Some 15 dilatations were outlined at the left base. Stereoscopic view indicated the presence of similar dilatations throughout both lungs.

ing as a rhinitis with copious nasal discharge. After several days, these symptoms receded, but he developed a deep though not irritating cough. He had no expectoration. He appeared slightly more dyspnoeic than previously and with some cyanosis. On fluoroscopy, there was observed a partial collapse of the left lung, a fact he had not suspected. The right lung was not collapsed. After several weeks, the left lung had reëxpanded. A small amount of pleural effusion developed during this time but soon disappeared. Several months later, vital-capacity determination showed a decrease from 2,000 to 1400 cc. Since the heart showed no evidence of enlargement, we felt this decrease in vital capacity was due to increase in the lung involvement. The basal-metabolism rate at this time was −22: repeated, it was −21. A preparation containing thyroid extract, gr. $\frac{1}{2}$ and pituitary extract (whole), gr. $\frac{1}{8}$, was given the patient three times a day for five days. It was discontinued because of diarrhoea, rapid pulse and dyspnoea.

On November 10, 1932, the patient again visited us. There had been no material change in his condition, except a steady and abnormal gain in weight, until about two weeks previous to his visit, when he became noticeably more dyspnoeic. His feet and ankles began to swell. An X-ray showed the heart to be very large, with great accentuation of vascular markings. There was temporary clinical improvement following digitalization, but he soon became much worse and died in his home December 12, 1932.

DIAGNOSIS

The question of the nature of the pathological process in the lungs which gave rise to these repeated pneumothoraces occasioned considerable speculation. Neither the symptoms, physical findings nor the X-ray appearance suggested pulmonary tuberculosis. The lung fields, in the X-ray film, showed greatly diminished aeration. The hilar regions were denser than normal. The lung markings were considerably accentuated and suggested pulmonary congestion or interstitial fibrosis. Viewed stereoscopically, there were many small, faintly visualized annular shadows, scattered throughout both lungs but more numerous at the bases. In order to determine the actual presence and character of these apparent dilatations, iodized oil was introduced into the bronchi. Several attempts failed to delineate any dilatations. Finally, iodized oil was introduced into the right base. An immediate film showed only the normal bronchial structure of the descending branches. After the film was exposed, the patient coughed quite hard five or six times. Another X-ray showed that although the patient had been in an upright position during the interval, the iodized oil had been transferred into the

left base by the act of coughing. In addition to the bronchial structure, which showed the normal, tapering outline, some fifteen circular dilatations were outlined at the left base (figure 2). These averaged about 5 mm. in diameter. From the appearance of all previous films, we judged that dilatations similar to these were present through both lungs and that the repeated pneumothoraces resulted from the thinning and rupture of some that were more superficially located.

In considering the type of pathological change present, the acquired type of bronchiectasis first came to mind. The absence of sputum throughout four years' observation and the failure to develop empyema following repeated perforation of pleura weigh heavily against pulmonary suppuration of any kind. "Dry bronchiectasis" has been suggested, but we feel that this condition is probably the same thing as congenital cysts of the lung. The dyspnoea, lack of cough or expectoration, evidence of cardiac embarrassment and eventual failure, as well as the character of the physical findings, were consistent with either of two conditions,—congenital cysts of the lung or emphysema. The form of the chest suggested the latter. However, emphysema is not common at the patient's age. The pulmonary engorgement and interstitial fibrosis, as delineated on the film, are not so marked in emphysema as was true in this case. The universal distribution of the dilatations does not rule out congenital cysts, as many such cases have been reported. The absence of superimposed infection during 22 years of life is possibly unusual but similar cases have been observed. Until the time of the postmortem examination, however, the diagnosis was still somewhat uncertain. Following is the pathological report by Dr. Emil Bogen, who performed the autopsy:

The body showed the juvenile or prepubertal conformation of Fröelich's syndrome, with soft, smooth skin, absence of hair over the body and only a little in the pubic region, with external genitalia smooth, small and underdeveloped. There was excessive nutrition, together with massive oedema of the extremities.

Puncture under water showed no air in the chest. The lungs were large and voluminous, and completely and densely adherent to the chest-wall throughout. On removal, a number of blebs or air-containing cavities were seen beneath the surface of both lungs, fairly evenly distributed.

On section, there were seen to be many shiny, smooth-walled, round cavities, varying in size from a pea to a filbert, often intercommunicating (figure 3). They were all empty, communicating with bronchi and free from gross inflammation or exudation. They were irregularly distributed throughout all five

lobes with little difference in their prominence in any area, except that they were somewhat more numerous in the peripheral portions, in the very apices, the diaphragmatic border and in the lingual tip of the left lung. There was normal-appearing lung tissue between the cysts with, however, a few small areas of atelectasis. There was no tuberculous involvement or pneumonic inflammatory area evident to gross inspection. The large vessels were slightly thickened. The hilar lymph nodes were greatly enlarged, especially the tra-

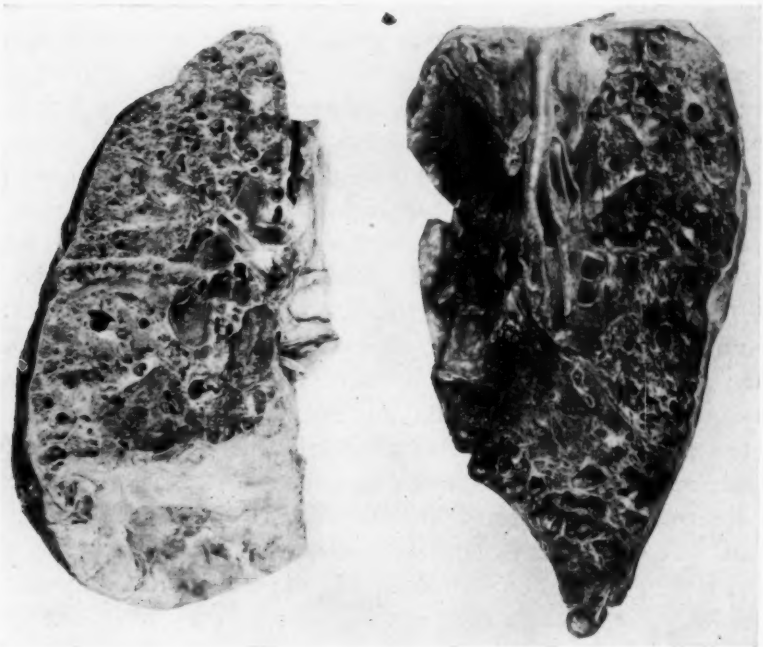

FIG. 3. Section through both lungs at autopsy showing numerous congenital cysts. The cysts were dry and air-containing, and communicated freely with the bronchi. The tracheobronchial lymph nodes were much enlarged, particularly in the right lung.

cheobronchials on the right side, which were gray, soft but resistant, homogeneous, and without any evidence of caseation, calcification or fibrosis.

The heart showed considerable dilatation of the right auricle and hypertrophy of the right ventricular muscle. The liver was enlarged and gave evidence of fatty degeneration. The kidneys showed foetal lobulation. The thymus was present and measured 3 x 4 cm. The thyroid, pituitary and adrenal glands were small; the parathyroids were larger than normal. The testes were small and appeared immature.

Histological Examination: The cysts in the lung communicated freely with the bronchioles, with each other, and with alveoli. The larger cysts were lined with flat and cuboidal epithelium; the smaller with cuboidal and columnar epithelium. The epithelial lining was absent in places but no exudate was seen. The walls were thin and composed of connective tissue mainly, but they contained smooth muscle fibres in some places. The crepitant areas of lung tissue between the cysts showed rather normal alveoli, somewhat distorted and irregular in size and shape. The capillaries were distended with blood.

The large tracheobronchial lymph nodes were composed of highly vascular lymphoid tissue. The cells stained less deeply than normal circulating lymphocytes. There was a notable absence of anthracosis.

Sections through the upper tracheal rings and the adjacent muscles showed scattered masses of thyroid tissue, discontinuous and separated by muscle and fibrous tissue. The thyroid alveoli varied in size and were distended with colloid material and lined with single layers of flattened or cuboidal epithelium.

The parathyroid consisted of densely packed groups of cells which were large, clear and with a relatively large amount of cytoplasm. The anterior lobe of the pituitary resembled the parathyroid in structure, but contained many eosinophilic cells. The tubules of the testes were shrunken, small and dense, devoid of lumina for the most part or the lumina were filled with fibrous material, and surrounded by a single layer of deeply staining oval or cuboidal cells. No spermatocytes, sperm-cells or spermatogonia were present.

PATHOLOGICAL DISCUSSION

The universal distribution of the cysts in the lungs and the absence of inflammatory reaction around them favor the diagnosis of congenital cystic disease. That this is equivalent here to foetal bronchiectasis is suggested by the presence of cuboidal epithelium and occasional columnar epithelium in the cysts, the presence of smooth muscle in their walls and the manner in which the cysts open on to one another similar to the opening of bronchioles on to one another. No actual cartilage was, however, seen in these walls. The presence of areas of atelectasis and of masses of alveolar cells without alveolar structure suggests that this condition may be a mechanical resultant of foetal bronchiectasis. In other words, the failure of the alveoli to form or open resulted in additional pull and air-pressure being exerted on the ends of the finer bronchioles and the atria, with the resultant formation of these cavities.

The increased resistance to circulation through the fibrotic tissue in the lung, with the thickening of the pulmonary arterial branches, accounts for the hypertrophic change in the heart. This eventuated in myocardial

failure, with acute passive congestion resulting in fatty degeneration of the liver. There had probably been some similar chronic process to account for the increased fibrosis in the spleen, with a terminal oedema in this organ.

The low basal metabolism might be explained by the small amount of thyroid tissue present in the scattered masses in the muscles around the trachea and larynx, as well as by the colloid changes found in these remnants. The small pituitary and atrophic testes are in keeping with the diagnosis of Froelich's syndrome. The apparently enlarged thymus was found on section to consist mainly of lymphoid tissue, and Hassall's bodies were not found.

The entire collection of endocrine anomalies is well in keeping with a diagnosis of congenital cystic disease of the lung since multiple congenital disturbances are often found associated.

In the light of these postmortem findings, all doubt of the condition being congenital cysts of the lung was removed. The history of never having been as robust as other boys during childhood, the character of the symptoms and physical findings and the association of other congenital anomalies are all quite consistent with this diagnosis.

CONGENITAL CYSTS OF THE LUNG

Until comparatively recently, this condition, also known as *congenital cystic degeneration of the lung, honey-combed lung, foetal bronchiectasis* and *cystic foetal bronchial adenoma*, was considered as occurring only very rarely. The first American case was reported by Pappenheimer in 1913. No additional cases were described in this country until 1925, when Koontz, in reporting a case observed by him, published an excellent review of the subject, collecting 108 European cases. Since this time, many instances of the condition have been discovered and reported. The chief difficulty in recognition lies in the fact that, in the absence of a superimposed infection, the patient may complain of practically nothing, even though there may be extensive cystic changes. Infection or, as in our case, pneumothorax, is often the thing which brings the condition to our notice. In the uncomplicated case, there may be slight dyspnoea on exertion but the patient is rarely conscious of this slight handicap since he has experienced it more or less from birth.

DIAGNOSIS

In the uninfected or uncomplicated case, the importance of the X-ray in diagnosis is undoubted. The larger, isolated cysts cast clear-cut

annular shadows with no perifocal reaction. Other parts of the lungs usually appear quite normal. In the smaller, disseminated cysts, as in our case, the annular shadows are not nearly so clearly delineated. Even with good stereoscopic films, the number of cysts which can be visualized is usually less than the number actually present. With free bronchial communication, iodized oil can be used to outline the cysts. The smaller cysts are undoubtedly harder to get to fill than the larger ones. When communication is blocked, the cysts appear on the film as circular opacities and must be differentiated from other types of cysts, nodular types of malignant tumor, certain types of tuberculosis, etc. The bronchovascular structure usually shows more or less accentuation, giving an appearance often described as "interstitial fibrosis."

Infection has already occurred, in the majority of cases, when the physician first sees the patient. The whole clinical picture then serves to focus attention on bronchiectasis as the probable cause. Differentiation must, at times, be difficult, if not impossible, during life. Location and distribution are of importance as most acquired ectasia are basal and bilateral, except when associated with upper-lobe pathological involvement, as in tuberculosis. The physical signs are probably not distinctive.

In the pathological specimen, the presence or absence of pigment in the tissues surrounding the cysts is stressed by many writers as of considerable importance in differentiation of congenital from acquired cysts. That this would hold in instances in which a blocking of the bronchi exists may be admitted but where there is really free communication, as in our case, one sees no reason for carbon particles from the air not being deposited in the cysts and being absorbed. The complete absence of anthracosis in all parts of the pulmonary structure in our case is attributed to the patient's residence in regions comparatively free from coal-smoke and not to the congenital nature of the pathological change.

TREATMENT

Single cysts which increase in size, due to valve-like action, and causing increasing dyspnoea and cyanosis, have been relieved by aspiration of air, in a few instances. Since pneumothorax is a possible result of this method of treatment, it would probably be used only in the most desperate situations. Many of these cases have ended fatally in spite of repeated aspiration. In the event of pneumothorax resulting from spontaneous rupture of a cyst, treatment should not differ from that of

pneumothorax from other causes. In the presence of infection, various methods have been used. Crosswell feels that lipiodol, instilled into the cysts, was of material benefit in restoring his patient to health. Moore's patient responded to repeated bronchoscopic aspirations and autogenous vaccine. Eloesser favors surgical treatment, and has secured good results by lobectomy or by thoracoplasty when there is free bronchial drainage. The uncomplicated case without infection requires no treatment.

SUMMARY

The literature regarding simultaneous, bilateral, spontaneous pneumothorax has been reviewed and 76 cases have been collected and studied. In 51 per cent of these cases, pulmonary tuberculosis was the causative factor: 21 per cent were "idiopathic" and 13 per cent due to emphysema. The mortality for the series was 65 per cent. Tuberculosis patients died in 85 per cent of the cases; less than one-fourth of the "idiopathic" cases terminated fatally. Only one proved case of perforation of the mediastinum was encountered, collapse in the rest being due to bilateral perforation. The ratio of males to females was four to one, a disparity equal to that in unilateral collapse.

An additional case of simultaneous, bilateral, spontaneous pneumothorax, observed by us, has been reported. The patient experienced bilateral collapse twice and unilateral collapse once, with complete reëxpansion each time; and eventually died of cardiac failure, secondary to congenital cysts of the lung, scattered widely through both lungs. Associated congenital anomalies were hypopituitarism, with a typical Froelich's syndrome, diabetes insipidus, hypothyroidism with unusual location and conformation of the thyroid, greatly underdeveloped testes, foetal lobulation of the kidneys, and parathyroid hyperplasia.

Some of the more recent literature on congenital cysts of the lung has been reviewed.

The authors are indebted to Drs. E. P. Smart and Emil Bogen who presented the films in this case at the 1932 and 1933 conventions of the National Tuberculosis Association. We also wish to thank Dr. H. F. Becker of Los Angeles, who observed this patient in his last illness and obtained permission for the postmortem examination.

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LEUCOCYTE COUNTS DURING ARTIFICIAL-PNEUMOTHORAX TREATMENT AND LUNG EXPANSION[1,2]

JOHN KENNETH DEEGAN

Investigators have shown that the leucocytes play important rôles in the pathogenesis of tuberculosis, and that the various changes in the tuberculous focus are reflected in the peripheral blood-picture. Thus the early pouring forth of mononuclear cells in tuberculous processes is reflected in an increase of these cells in the peripheral blood-stream at this time. As the tubercle progresses, and breaks down to form abscesses, the polymorphonuclear cell dominates the pathological picture, and is so depicted by an increase of these cells in the differential blood-count. Healing of tubercle is characterized, first, by an increased inflow of lymphocytes and then by a secondary inflow of the mononuclear cells, which changes are likewise found in the peripheral blood-picture. Although it was known that these cells were identified with definite stages of tubercle development, the interpretation of the blood-picture was for some time a matter of debate, since the typical clinical case harbored the disease in various stages of development—infection, ulceration, healing—and all of these stages were reflected in the blood-stream. It remained for Medlar to clarify the situation by pointing out "that there is no specific leucocyte reaction for the disease as a whole, but rather a type of leucocytic reaction indicating the different stages of the process," and that "because of the complexity of the disease, it is necessary to consider the total leucocyte count together with the differential percentages." As a basis of comparison Medlar established a normal standard for white cell count and differential:

		per cent
Total count	6,000–9,000	100
Polymorphonuclears	Seldom above 5,000	50 to 65
Lymphocytes	Seldom below 2,000	25 to 39
Mononuclears	Seldom above 700	6 to 9

[1] From the William Wirt Winchester Hospital and Yale School of Medicine, New Haven, Connecticut.

[2] Presented at the twenty-ninth annual meeting of the National Tuberculosis Association, Toronto, Ontario, June 29, 1933.

Medlar then classified the leucocytic picture in tuberculosis as follows:

TYPES	WHITE BLOOD CELLS	POLYMORPHONUCLEARS	LYMPHOCYTES	MONONUCLEARS
Septic type, Abscess-formation. New tubercle-formation if mononuclears above 9 per cent.....	Usually above normal. May have leucocytosis or leucopoenia	Above 65 per cent (70 per cent or more)	Below 25 per cent	Usually above 8 per cent
Hyperplastic type, New tubercles formed but not undergoing abscess-formation. 30 per cent lymphocytes = healing tendency.....	Normal limits	Below 60 per cent	25 per cent or more	Above 10 per cent
Nonseptic type.....	Never over 10,000	Lymph per cent = or exceeds polys per cent		Below 10 per cent

The above interpretations of Medlar were used in studying the leucocytic picture in 52 cases of far-advanced pulmonary tuberculosis subjected to artificial-pneumothorax treatment and other forms of collapse therapy in whom the collapsed lung subsequently was allowed to expand.

TECHNIQUE

Free-flowing blood was taken from the finger, diluted twenty times, well shaken immediately and again before counting. Four corner squares of the chamber were counted. The differentials were made on glass slides, a drop of blood on one slide being allowed to spread beneath the edge of a second slide applied at a sharp angle and then swept rapidly and evenly over the first slide. Wright's stain was used. Two hundred cells were counted in each smear and the differential recorded. In the main more than 95 per cent of the total and differential counts were done by one technician. The remaining counts were secured through the coöperation of the physicians in charge of former patients and the kindness of the staffs at other sanatoria. Cells were classified as neutrophiles, lymphocytes (large and small), mononuclear cells (monocytes, transitional cells, epithelial leucocytes and large mononuclear cells), eosinophiles and basophiles. No subdivision of polymorphonuclear cells into segmented and nonsegmented forms was made.

In all, 1,040 counts were done on 52 cases of far-advanced tuberculosis over a period of four years. All new cases underwent an initial blood study and, following the institution of collapse therapy, repeated studies at intervals varying from one week to one month while hospitalized, and at longer intervals after discharge. The clinical progress of the case was followed by a temperature, pulse and respiration record, physician's progress notes, physical examination and roentgenograms every two months while hospitalized. Discharged cases were followed through local physicians and at the outpatient department of the hospital.

The 52 patients comprised 20 males and 32 females, ranging in age from 14 to 61 years. Twenty-nine of them were from 20 to 30 years old. Classified on admission according to the National Tuberculosis Association standards, the 52 cases fell into the following groups: FA-1, 5; FA-2, 19; FA-3, 28. The tuberculous process was unilateral in 14 cases (all with cavity-formation) and bilateral in 38. Cavity-formation was evident unilaterally in 37 cases, bilaterally in 9 and absent in 6. The cases were treated with artificial pneumothorax for varying periods of time from 4 to 46 months. The treatment was terminated for various reasons,—deliberate reëxpansion under clinical control, reëxpansion through adhesions drawing out the lung, substitution of other forms of collapse therapy (thoracoplasty and phrenicoexairesis), failure to secure adequate collapse, spread of disease to previously unaffected portions of the same or opposite lung, failure of the patient to coöperate in continuing treatment after discharge from the hospital, etc.

Some objection might be made to classifying as reëxpanded a lung previously collapsed by pneumothorax, for which later a thoracoplasty had been substituted. However, it is felt by the author that a lung so treated reëxpands after thoracoplasty within the limits of the altered thoracic cage.

Attention is called to the uniformly high initial total counts as indicative of the severity of the infection on first examination. The tables which follow present only the initial and latest count in the individual case. It is hoped that these two counts will suffice in indicating the trend followed by the blood-picture in the various instances. It is appreciated that for adequate study numerous successive counts must be evaluated in each case, but space does not permit the presentation of such extensive data.

If we examine group FA-1 we find that 4 cases presented unilateral cavitation and had septic blood counts on admission. Table 1 gives the

initial and latest counts in cases of this group. These 4 cases were successfully treated with artificial pneumothorax which resulted in the closure of the cavities, and subsequent loss of symptoms. Concurrently the blood count changed to the nonseptic type in three of the cases. In the fourth case (A.W.) the blood count showed a decided tendency to

TABLE 1

FA-1

CASE	WHITE BLOOD CELLS	POLYMORPHONUCLEARS	LYMPHOCYTES	MONONUCLEARS	A.P. DURATION	OBSERVATION PERIOD
					months	*months*
E. D.	14,100	62	27	11	24	28
	8,650	45	44	11		35
S. H.	11,800	65	27	8	23	35
	9,600	50	43	7		
S. H.	11,500	60	27	11		
	9,800	46	43	11		
A. S.	14,400	63	27	10	27	35
	6,650	60	37	3		
A. W.	12,400	64	26	9	6	15
	8,400	63	25	12		
M. S.						
11/26/28	10,000	58	30	10	1st admission	
8/13/30	5,150	52	38	8	2nd admission A.P. left	
8/26/30	9,000	70	24	6	Clinical and X-ray	
9/ 2/30	9,800	64	27	9	spread to right	
9/ 8/30	9,800	68	29	3		
9/15/30	10,300	63	28	9		
9/23/30	9,800	67	27	6	A.P. right	
10/ 7/30	8,200	64	28	8		
10/14/30	9,400	60	30	10		
10/27/30	10,000	60	30	10		
12/12/30	8,000	65	27	8		
2/ 1/33	10,500	62	29	9		

become less septic but it still remained septic. One of these cases (S.H.), a woman of 61, returned to her household duties with such vigor that after a little more than a year there was a slight return of symptoms,—cough, slight expectoration, positive sputum and the blood count reverted to the septic type. Roentgenograms taken at this time showed a spread

to a previously uninvolved portion of the collapsed lung. She was persuaded to reënter the hospital, where after adequate study pneumothorax was abandoned and a phrenicoexairesis employed. Clinical improvement resulted, the patient lost all her symptoms and was again discharged to her home July 31, 1932. Warned by the previous break she has learned to live within her limitations and has shown continued clinical improvement, with a reversion to and maintenance of a nonseptic type of blood count.

The other of group FA-1 (M.S.) presents some interesting features. On first admission November 26, 1928, the patient presented a blood count of 10,000 white cells with 58 per cent polymorphonuclears, 30 per cent lymphocytes, and 10 per cent mononuclear cells. The pulmonary disease at this time was limited to an old inactive infiltration scattered above the 4th rib and 8th dorsal spine on the right side, with an active infiltration in the outer 2nd interspace on the left. The patient did well on bed-rest, and after a hospital residence of seven months was discharged as clinically arrested, the lesion in the 2nd interspace on the left having disappeared. Roentgenograms of July 2, 1930, showed the reappearance of a small lesion with an area of rarefaction in its centre in the left 2nd interspace. On bed-rest the temperature varied between 98° and 99.4°, pulse and respirations were normal. Cough and expectoration of 2 to 10 cc. of mucopurulent sputum continued daily. Roentgenograms on August 12, 1930, showed a slight increase in the process in the left 2nd interspace, and it was decided to try artificial pneumothorax on that side. Initial pneumothorax on the left on August 16 resulted in a selective collapse of the upper lobe. Cough, however, was increased. A roentgenogram on August 27, 1930, showed a marked increase in the shadows on the right side from the 1st rib to the interlobar fissure. Another roentgenogram on September 17 showed no improvement in this new shadow on the right, and possibly an antrum in its centre. Artificial pneumothorax was instituted on the right side September 23, 1930. Improvement from that date was rapid. The last positive sputum was obtained on October 8, 1930. The patient was discharged to another institution late in December, 1930, and left there against advice in November, 1931. Both lungs were allowed to reëxpand following this episode. The patient was seen occasionally in the outpatient department and continued to do well. On February 1, 1933, she reported for examination owing to an attack of influenza suffered the latter part of the previous month. No signs of active pulmonary disease could be

found anywhere in the lungs and the roentgenograms taken on this date showed a remarkable clearing of the shadows as compared with previous films. The only residuum was an interlobar thickening of the fissure on the right side. The low total white cell count and good differential on August 13, 1930, are especially significant in view of the changes in the count on August 26, 1930, which preceded the clinical and the X-ray evidences of extension of the disease to the opposite apex. The importance of this shift of the differential to a septic type in cases with normal totals has been emphasized by Oatway who found that 64 per cent of tuberculous cases with normal total counts are really septic in type because of the abnormal differential. Other investigators have shown that the total white cell count may vary as much as 50 per cent in normal individuals in a space of 30 minutes, whereas the differential count has a normal variation of only 10 per cent in the healthy subject. Medlar states that the average shift of the differential in cases sick with tuberculosis is but 7 per cent within 30 minutes. It is noted that in this case the succeeding counts showed an increasing tendency toward the septic type and were altered by the institution of bilateral simultaneous pneumothorax on September 23, 1930. At the time of discharge to another institution the patient had a blood-picture that might be characterized as normal. The count obtained on February 1, 1933, might possibly have been influenced by the attack of influenza the month before. An effort is being made to keep in contact with the patient to watch developments.

All five cases of group FA-1 are clinically classified as arrested and are working.

In group FA-2 total counts and differentials were in harmony as a rule with the clinical course of the individual case. The accompanying table 2 gives the initial and latest counts of the 19 patients who were admitted with this classification. Twelve were discharged as arrested, one of whom (case H. H.) has since become active again. One case (C. B.) in this group was discharged as improved and one as unimproved (case E.M.). Five cases have had thoracoplasty performed because of failure of the artificial pneumothorax to secure desired results; four of the thoracoplasty cases are still under sanatorium care; one has been discharged as clinically arrested. Surgical intervention consisted of unilateral artificial pneumothorax in 14 cases, two of which were supplemented by phrenicoexairesis, and 5 cases of unsuccessful unilateral artificial pneu-

TABLE 2

FA-2

CASE	WHITE BLOOD CELLS	POLYMORPHONUCLEARS	LYMPHOCYTES	MONONUCLEARS	A.P. DURATION	OBSERVATION PERIOD
					months	*months*
J. A.	11,000	76	16	8	40	58
	12,600	62	27	11	Sinusitis and otitis media	
E. B.	11,000	70	23	7	11	34
	8,800	57	34	9		
B. I.	15,400	66	26	8	30	36
	14,600	64	25	11	Chronic endometritis	
I. B.	10,000	73	20	7	20	44
	7,400	56	38	6		
A. B.	13,200	66	20	14	10	23
	8,200	63	27	10		
K. H.	10,600	73	19	8	12	52
	8,800	63	28	9		
H. H.	13,600	72	19	8	39	53
	11,800	62	27	11		
	12,300	69	18	13		
A. M.	18,050	78	6	12	46	48
	8,000	60	28	12		
R. R.	10,400	68	18	14	14	57
	7,950	60	30	10		
C. R.	17,750	63	25	12	10	30
	11,900	52	34	14		
S. R.	17,600	68	20	10	39	55
	8,800	65	24	11		
R. S.	13,600	70	24	6	19	23
	10,000	58	36	6		
C. B.	15,100	70	20	10	20	35
	9,000	60	27	13		
E. M.	16,600	72	16	12	26	28
	15,000	64	20	14		

TABLE 2—*Concluded*

CASE	WHITE BLOOD CELLS	POLYMORPHONUCLEARS	LYMPHOCYTES	MONONUCLEARS	A.P. DURATION	OBSERVATION PERIOD
					months	*months*
R. A.	15,300	61	25	14	19	27
	21,600	75	12	13		
A .G.	14,600	65	21	12	24	31
	12,300	75	15	9		
O. U.	13,800	69	22	9	12	38
	7,800	75	22	4		
V. S.	12,800	69	14	9	7	10
	8,400	73	19	7		
H. S.	11,600	73	18	8	13	25
	7,600	61	30	9		

mothorax which were abandoned in favor of thoracoplasty. There were no bilateral pneumothoraces in group FA-2. A brief résumé of these cases follows:

Case J. A.: Admitted with septic count which was maintained throughout the course of her treatment and subsequent observation. Pneumothorax was continued for a period of forty months and the patient has been followed for a period of fifty-eight months. Clinical improvement has been striking but there has been no relief from a chronic sinusitis and otitis media, which have persisted. Patient is now working.

Case E. B.: Admitted with a diagnosis of far-advanced pulmonary tuberculosis and tuberculous enteritis. The left lung was involved. Pneumothorax was continued for a period of eleven months with entire relief of symptoms. Patient has been under observation for thirty-four months. The blood count has shifted from a septic to a nonseptic type.

Case B. I.: The lung was held collapsed for a period of thirty months following admission with rather extensive disease on the right side. Clinically the tuberculosis has been arrested for more than twenty-four months and the lung has been allowed to reëxpand. The blood-picture has remained septic in type, possibly due to a chronic endometritis.

Case I. B.: Patient had unilateral disease with cavitation. Pneumothorax was maintained for a period of twenty months, after which the lung reëxpanded as a result of adhesions. Phrenicoexairesis was done to maintain the good result incident to pneumothorax. The blood count changed from septic to nonseptic type, and has so continued.

Case A. B.: There was unilateral cavitation in the right upper lobe. After pneumothorax had been maintained for ten months the lung began to reëxpand. Oleothorax was instituted and has been maintained for a period of thirteen months. Blood-picture has remained septic but is better.

Case K. H.: The disease was unilateral and complicated by a pleural effusion. The fluid was withdrawn, replaced with air and the pneumothorax maintained for twelve months. The patient's clinical condition improved, as did the blood count, which, however, is still septic.

Case H. H.: Patient presented bilateral disease with cavitation on the left. Pneumothorax was maintained on the left side for a period of thirty-nine months. The clinical condition became excellent and the symptoms disappeared. The lung was allowed to reëxpand. The patient returned to work but after one year an acute exacerbation occurred in the contralateral lung and she is again curing. It was noted that the patient continued to run a septic blood-picture during the entire course of her hospital residence, and that at the time of discharge the count was 11,800: 62 per cent polymorphonuclear cells; 27 per cent lymphocytes; 11 per cent mononuclear cells. The relapse was accompanied by further unfavorable changes in the blood-picture.

Case A. M.: There was far-advanced pulmonary tuberculosis with cavitation on the right side. An excellent pneumothorax collapse was accomplished on the right and maintained for forty-eight months. The blood-picture changed from septic to a hyperplastic type during the course of treatment and has thus continued. The fluid-reaction incident to the expansion of the lung was accompanied by no material changes in the hyperplastic picture.

Case R. R.: Unilateral pulmonary tuberculosis with extensive cavitation. The septic type of blood-picture changed to a hyperplastic type under pneumothorax, which was maintained for fourteen months. Patient has been observed for fifty-seven months and has been working for the past three years.

Case C. R.: Admitted with bilateral tuberculosis with cavitation in the right lung. The blood-picture was of the septic type. Pneumothorax maintained for ten months on the right with a change of blood-picture to one of less septic type. The patient discontinued treatment against advice after but ten months. She was heard from intermittently during the succeeding twenty months. No examination was made during this period but the clinical progress was good.

Case S. R.: Unilateral far-advanced tuberculosis with extensive cavitation in the right upper lobe. Pneumothorax treatment was instituted with strikingly beneficial result and was maintained thirty-nine months. During this period the blood count became less septic in type and has remained the same throughout sixteen months of additional observation. No material change in the blood-picture was observed incident to pleural effusion during reëxpansion of the lung.

Case R. S.: Bilateral pulmonary tuberculosis with cavitation on the left. Pneumothorax treatment of the left lung was maintained nineteen months with clinical improvement and change in the blood-picture to a nonseptic type.

Case C. B.: Far-advanced fibrocaseous type of disease with cavitation of the right lung. Pneumothorax on the right was maintained for twenty months, during which time the patient improved clinically and the blood-picture changed from a septic to a hyperplastic type. Patient discharged as improved.

Case E. M.: Admitted with unilateral tuberculosis and cavitation of the right upper lobe. Pneumothorax was maintained during twenty-six months, at the end of which time the patient was lost to sight. Clinically he improved under the treatment but was subject to relapses. Blood count was always septic in type. Indirect information is to the effect that the lung has re-expanded and that the patient is curing at home.

Case R. A.: Admitted with far-advanced bilateral pulmonary tuberculosis with extensive cavitation of the left apex. Pneumothorax was carried on the left side during nineteen months, when it was discontinued because of adhesions preventing the adequate collapse of the cavity. A thoracoplasty was advised eight months later. The septic type of blood count was maintained throughout, although the clinical condition of the patient was markedly improved. The sputum was constantly positive.

Case A. G.: Bilateral pulmonary tuberculosis with cavitation on the left. Pneumothorax was carried twenty-four months on the left side when it was discontinued and the lung was allowed to reëxpand. Thoracoplasty was performed with some clinical improvement but the sputum is still positive and the septic type of blood-picture is maintained.

Case O. U.: Far-advanced pulmonary tuberculosis, unilateral. Pneumothorax on the right was maintained twelve months when it was discontinued in favor of thoracoplasty. The patient showed no material clinical change as a result of the major operation and still continues a septic differential count although the total white cell count has been materially lowered.

Case V. S.: Extensive unilateral tuberculosis throughout the left lung. Pneumothorax treatment was maintained seven months when it was discontinued in favor of thoracoplasty. The patient has shown some slight clinical improvement as a result of the major operation. The temperature, pulse and respiration have been normal and the sputum negative but the septic type of blood count persists. The prognosis is guarded.

Case H. S.: Unilateral pulmonary tuberculosis with cavitation. Pneumothorax on the right maintained thirteen months and then discontinued in favor of thoracoplasty. An excellent clinical result was obtained. The patient discharged as clinically arrested. The blood has improved considerably but is still within the septic range if the standards are rigidly interpreted. It

might also be considered a change to the hyperplastic type under a slightly more liberal interpretation of the standards.

Of 19 cases in class FA-2, twelve were discharged as clinically arrested: three of these cases changed from an initial septic type of blood-picture to a nonseptic type; two assumed the hyperplastic type; and four by strict interpretation remained septic in character but to a less severe degree than on admission. One case of oleothorax discharged as clinically arrested showed a decided improvement in the blood-picture in that it became less septic. Two of the cases discharged as clinically arrested showed a septic type of blood-picture throughout the course of treatment, and it was thought that conditions other than tuberculosis, such as chronic sinusitis, otitis media, chronic endometritis, were responsible for the high total counts and septic type of differentials in these instances. One case (H. H.), discharged as clinically arrested, is now curing again; it is interesting to note that the patient maintained a relatively high septic type of blood-picture throughout the initial course of treatment although markedly improved clinically and roentgenologically. One case on discharge was classified clinically as improved and, although working at present, occasionally raises positive sputum despite continued roentgenological and clinical improvement. This patient maintains the hyperplastic type of blood-picture as compared with the initial septic one. One patient, discharged as unimproved, maintained a septic type of blood-picture during his stay in the hospital; he refused further operative interference and discontinued the artificial pneumothorax against advice. Five patients, who did not improve under pneumothorax treatment and who persistently showed a septic type of blood-picture, underwent thoracoplasty. Major surgery resulted in one of these cases (H. S.) being discharged as improved, the septic type of blood-picture having become less severe in character. The other four, while clinically benefited by the operation, are still hospitalized and show septic counts. In some of the four it is felt that the disease in the contralateral lung as well as that in the lung subjected to thoracoplasty may possibly influence the blood-picture.

Twenty-eight cases are included in group FA-3. Table 3 shows the initial and final counts in each of these cases, together with the duration of administration of pneumothorax and observation of the individual.

Case E. C.: Admitted July 16, 1929. Pneumothorax started July 26, 1929, on the left side because of extensive cavitation confined to the upper lobe.

TABLE 3

FA-3

CASE	WHITE BLOOD CELLS	POLYMORPHO-NUCLEARS	LYMPHOCYTES	MONONUCLEARS	A.P. DURATION	OBSERVATION PERIOD
					months	*months*
E. C.	14,100	75	18	7	24	46
	8,000	50	45	5		
T. D.	16,000	60	30	6	6	44
	6,350	67	26	7		
M. J.	14,800	64	25	11	19	41
	6,500	49	42	8		
C. Mc.	16,100	65	33	2	14	44
	9,400	57	34	9		
E. P.	15,000	72	15	12	44	59
	9,200	62	24	14		
D. B.	11,200	69	24	7	17	39
	10,200	56	32	12		
J. E.	12,900	70	22	8	18	44
	13,700	57	28	15		
R. H.	12,000	67	22	11	12	37
	11,900	59	35	3		
E. H.	14,000	68	18	14	8	14
	11,900	68	16	16		
M. K.	17,000	70	19	8	rt. 12	36
	17,400	70	12	18	lf. 17	
M. W.	16,700	63	24	6	4	12
	13,100	73	19	6		
R. M.	15,000	70	23	7	39	54
	11,050	70	22	6		
H. F.	17,000	80	15	5	lf. 25	41
	9,200	65	27	8	rt. 10	
W. H.	11,200	74	17	9	37	45
	6,400	67	26	4		
J. M.	17,000	82	12	6	23	51
	12,600	60	29	11		

TABLE 3—*Concluded*

CASE	WHITE BLOOD CELLS	POLYMORPHONUCLEARS	LYMPHOCYTES	MONONUCLEARS	A.P. DURATION	OBSERVATION PERIOD
					months	*months*
J. S.	16,200	70	18	12	15	26
	14,200	68	20	12		
I. Z.	11,600	57	27	13	4	16
	12,200	67	22	10		
B. F.	11,600	60	25	13	8	15
	10,000	56	23	20		
	15,800	73	16	11		
E. G.	14,400	70	22	8	lf. 10	13
	23,800	68	16	20	rt. 6	
J. K.	13,400	69	19	12	lf. 8	23
	15,000	66	21	13	rt. 4	
G. K.	16,400	74	16	10	4	6
	19,600	80	13	7		
T. M.	15,000	69	19	12	9	15
	15,000	67	17	16		
H. M.	12,300	65	23	12	18	26
	17,800	67	17	16		
M. M.	17,400	70	20	10	7	12
	16,200	76	14	10		
C. M.	13,400	66	22	12	5	9
	12,200	66	18	16		
C. S.	17,800	68	19	13	9	20
	13,800	84	4	12		
P. T.	15,800	70	16	11	4	9
	22,200	80	2	18		
J. W.	14,500	75	13	12	lf. 20	28
	13,300	68	20	7	rt. 4	

The collapse was maintained for twenty-four months. The patient has been under observation forty-six months. During that time the initial septic count changed to a nonseptic type. The patient had a complicating pleural effusion during the course of treatment but this did not materially affect the blood-picture.

Case T. D.: Admitted May 23, 1929. Far-advanced pulmonary tuberculosis bilateral with cavitation in the right upper lobe. Artificial pneumothorax was started on the right June 6, 1929. Because of adhesions phrenicoexairesis was performed on the right September 17, 1929. The patient developed a tuberculous empyema September 28, 1929, with a resulting more septic type of blood-picture. Pneumothorax was discontinued after six months because of fluid reaction and empyema. The patient did well clinically on routine sanatorium treatment and became asymptomatic. The septic type of picture gradually changed to one of less severe degree. The patient has been under observation forty-four months, the last twelve of which he has been working.

Case M. J.: Admitted December 27, 1929, with far-advanced pulmonary tuberculosis and cavitation of the right lung; and scattered infiltration throughout the left lung. Pneumothorax was initiated on the right on January 21, 1930, and maintained nineteen months. A pleural effusion which developed November, 1930, did not materially change the blood-picture. The patient gradually improved clinically, and the blood-picture changed from a septic to a nonseptic type which has been maintained.

Case C. Mc.: Admitted September 1, 1929. Far-advanced pulmonary tuberculosis on the left with cavitation of the left upper lobe. Pneumothorax was started on the left September 15, 1929, and continued for 14 months. The patient improved very much clinically and the blood-picture changed to a nonseptic type which has been maintained. The patient has been under observation forty-four months.

Case E. P.: Admitted June 27, 1928. Far-advanced pulmonary tuberculosis; scattered infiltration throughout both lungs with cavitation of the left lung. Pneumothorax was begun on the left July 5, 1928, with excellent clinical result. Fluid developed in April, 1929, but did not materially alter the blood-picture. Phrenicoexairesis was done on June 19, 1929. Pneumothorax was discontinued after a period of forty-four months. Patient was in excellent clinical condition on discharge. The blood-picture while showing a gratifying improvement is still septic in type. Total length of time under observation fifty-nine months.

Case D. B.: Admitted January 4, 1930, with far-advanced pulmonary tuberculosis and cavitation of the left lung. Pneumothorax was started on the left January 14, 1930. The collapse was unsuccessful owing to adhesions and was supplemented by phrenicoexairesis on September 23, 1930. The patient developed tuberculous empyema with an increasing septic blood count. He was discharged improved, but against advice, on June 26, 1931, and subsequently discontinued the pneumothorax treatment. He is at present working and refuses to be examined but did consent to have blood study which showed a hyperplastic type of blood count. He states that he is asymptomatic.

Case J. E.: Admitted September 17, 1929. Far-advanced bilateral pulmo-

nary tuberculosis with bilateral cavitation. Pneumothorax was begun on the left August 16, 1930, and continued eighteen months. Phrenicoexairesis was done on the right January 25, 1930. The patient improved clinically with these procedures but continues to raise positive sputum. Clinical condition is fair but the patient must continue to cure. The septic type of blood count has been maintained throughout.

Case R. H.: Admitted April 9, 1930, following a spontaneous pneumothorax on the left side the previous month with development of tuberculous empyema. Fluid was removed and the collapse maintained with artificial pneumothorax until April 21, 1931, when an attempt was made to reëxpand the lung. There was an extension to the right lung in September, 1931, with cavitation developing rapidly in the new area affected. Phrenicoexairesis was performed on the right side December 3, 1931. There was remarkable clinical improvement and the sputum became negative February 5, 1932. The patient has done very well clinically but has been advised to continue curing. Although the blood-picture has shown some tendency to recede from the septic type it is nevertheless definitely septic in character.

Case E. H.: Admitted September 16, 1932, after pneumothorax treatment since March 29, 1932, by a private physician. The cavities in the right lung were not affected by the pneumothorax, and accordingly the treatment was abandoned on November 14, 1932. The patient has done poorly from a clinical standpoint and has suffered an exacerbation in the left lung. The septic type of blood-picture on admission has been maintained.

Case M. K.: First admitted May 29, 1930. Far-advanced pulmonary tuberculosis with cavitation on the right side. Pneumothorax was begun on the right June 7, 1930; abandoned June 1, 1931. Meanwhile the disease had spread to the left lung, and pneumothorax had been started on that side, April 20, 1931. The pathological involvement steadily increased, and finally the pneumothorax on the left was also abandoned, September 6, 1932. The patient has continued a septic type of blood-picture throughout her entire course and clinically has shown progressive disease.

Case M. W.: Admitted May 10, 1932, with extensive cavitation of the left lung. Artificial pneumothorax was initiated on the left May 12, 1932. Discharged to State Sanatorium July 19, 1932, and left the latter institution against advice after two months. The blood-picture during the course of treatment was septic in character. The patient continued at home for six months, growing rapidly worse, and finally was admitted to a third institution with a clinical spread of the disease and still showing a septic type of blood count.

Case R. M.: Admitted November 11, 1928, with far-advanced bilateral tuberculosis and cavitation on the left. Artificial pneumothorax was begun on the left, February 15, 1929. Phrenicoexairesis was performed on the left,

June 21, 1929. Artificial pneumothorax was abandoned, May 30, 1932. There has been a general clinical improvement, but constantly positive sputum throughout illness. The patient continues to "cure" and has maintained a septic type of blood-picture throughout the period of observation.

Case H. F.: Admitted December 29, 1929. Far-advanced pulmonary tuberculosis with bilateral cavitation, especially on the left. Pneumothorax was instituted on the left January 3, 1930, and maintained for twenty-five months when it was terminated in favor of thoracoplasty. Meanwhile pneumothorax was begun on the right on March 17, 1931, and maintained ten months, during which interval the patient underwent the thoracoplasty on the left side. The patient was greatly improved by the collapse therapy to which she was subjected and is at present at home. Under the influence of bilateral simultaneous pneumothorax the septic blood-picture on admission gradually changed to a nonseptic type as evidenced by a prethoracoplasty total count of 8,000 white cells and a differential count of 46 per cent polymorphonuclear cells, 42 per cent lymphocytes and 12 per cent mononuclear cells. Since the major operation the blood-picture has again reverted to a septic type although the patient is asymptomatic and continues to show clinical improvement.

Case W. H.: Admitted August 24, 1929. Far-advanced pulmonary tuberculosis. Pneumothorax had been instituted by a private physician on August 16 to control profuse haemoptysis. Pneumothorax was maintained for thirty-seven months when it was terminated in favor of thoracoplasty. The blood count gradually improved and has become less septic during the observation period of forty-five months. He is at present classified as arrested.

Case J. M.: Admitted February 7, 1929. Far-advanced pulmonary tuberculosis with cavitation on the right. Pneumothorax on the right was started February 12, 1929, maintained for twenty-three months and then was discontinued in favor of thoracoplasty. The patient has done extremely well clinically. It is interesting to note that the total count has never been below 11,100. The septic type of differential has gradually changed to the hyperplastic type which is maintained. The patient has been working for more than a year with no ill effects.

Case J. S.: Admitted March 28, 1931. Far-advanced pulmonary tuberculosis bilateral with extensive cavitation on the left. Pneumothorax started on the left April 6, 1931, and was supplemented with phrenicoexairesis on May 25, 1931. There was a marked clinical improvement afterward, but positive sputum continued and the cavity on the left was thought to be still patent. A thoracoplasty was substituted for artificial pneumothorax after fifteen months. The patient lost all symptoms, but abnormal signs persisted in the contralateral lung. She was discharged as improved and has continued to cure at home. The blood-picture has remained of the septic type throughout her entire course.

Case I. Z.: Admitted January 28, 1932, with extensive bilateral pulmonary tuberculosis and atelectasis of the right lung. Pneumothorax on the right instituted February 23, 1932, and discontinued after four months in favor of thoracoplasty. The patient failed to show any improvement following the major operation and is at present hospitalized. The blood count remained of the septic type throughout her entire course.

Case E. F.: Admitted September 15, 1931, with extensive pulmonary tuberculosis and cavitation on the right side. Pneumothorax begun on the right September 28, 1931, with fairly good clinical result. However, the patient's blood count continued to present a septic picture and on January 16, 1932, the total count was 10,000 cells, 58 per cent polymorphonuclears, 23 per cent lymphocytes, 20 per cent mononuclear cells. On May 14, 1932, the patient suffered a spontaneous pneumothorax on the right with extension to the left which necessitated abandonment of the pneumothorax on the right. The patient died December 16, 1932.

Case E. G.: Admitted November 6, 1929, with bilateral pulmonary tuberculosis and bilateral cavitation. Bilateral pneumothorax was instituted and maintained on the left side for ten months and on the right side for six months before being discontinued. Patient was not improved by collapse therapy, continued to run a septic type of blood count, and died December 16, 1930.

Case J. K.: Admitted June 11, 1929, with bilateral pulmonary tuberculosis and bilateral cavitation and tuberculous enteritis. Bilateral pneumothorax was instituted, that on the left being maintained for eight months, that on the right for four months. The patient's clinical course was down-hill. He continued to show a septic type of blood count throughout and finally died May 3, 1931.

Case G. K.: Admitted October 16, 1929, with far-advanced pulmonary tuberculosis and cavitation on the left side. Pneumothorax was started on the left October 28, 1929, and was immediately complicated by fluid reaction. The pneumothorax was continued for only four months when the lung was allowed to reëxpand because the disease was increasing on the opposite side. The septic type of blood count persisted to death on May 8, 1930.

Case T. M.: Admitted February 4, 1930, with far-advanced pulmonary tuberculosis bilateral with cavitation on the right. Pneumothorax was started on the right on February 17, 1930. The initial refill was followed by a spontaneous collapse of the lung, succeeded in turn by a tuberculous empyema. Pneumothorax was continued up to the time of discharge in November, 1930, when it was abandoned. The patient returned to Italy and subsequently died. The clinical course was slowly down-hill and the blood-picture was constantly septic in type.

Case H. M.: Admitted August 27, 1930, with extensive tuberculosis and cavitation of the left lung. Pneumothorax was started on the left on September 2,

1930. The patient showed a slight clinical improvement up to the time of extension of disease to the contralateral lung in March, 1931. The initial spread was fairly well tolerated by the patient but succeeding involvement of the right lung finally forced a discontinuance of the pneumothorax. The patient was discharged to her home June 10, 1932, where she died three months later. The septic type of blood-picture continued throughout the entire illness with increases attending the new involvements of the right lung.

Case M. M.: Admitted July 3, 1929, because of spontaneous pneumothorax which was continued as an artificial pneumothorax. The patient failed to do well and the pneumothorax was abandoned early in January, 1930. The patient died suddenly (cardiac) February 27, 1930. The blood-picture was always of the septic type.

Case C. M.: Admitted April 27, 1931 with extensive tuberculosis and cavitation of the left lower lobe. Pneumothorax was begun on the left on June 27, 1931, and supplemented by phrenicoexairesis on the left July 24, 1931. The pneumothorax was abandoned in November, 1931. The patient died January 3, 1932. There was a septic blood-picture throughout the entire time.

Case C. S.: Admitted July 3, 1930. Extensive disease throughout the right lung with cavitation in the upper lobe. Pneumothorax was started on the right on July 11, 1930. The collapse was ineffective and phrenicoexairesis was performed October 8, 1930. The patient was discharged to a State Institution November 22, 1930, where, after six months more of pneumothorax treatment, the latter was abandoned as noneffective. The patient died March 14, 1932. The blood-picture was of the septic type throughout the entire course.

Case P. T.: Admitted October 13, 1931, with extensive disease throughout both lungs, and cavitation on the left. Pneumothorax, begun on the left on October 26, 1931, was complicated by fluid in December, 1931. The patient was discharged to a State Institution April 5, 1932, where he died after three months. The duration of the pneumothorax was four months. The septic type of blood-picture continued throughout.

Case J. W.: Admitted May 9, 1930, with far-advanced bilateral pulmonary tuberculosis and bilateral cavitation. Bilateral pneumothorax was instituted. On the right side the pneumothorax was discontinued after a four months' trial, on the left side after twenty months. The patient did poorly, showed progressive disease and finally died in September, 1932. The blood-picture was always of the septic type.

Of the 28 cases in group FA-3, five were discharged as clinically arrested. Of these 5 cases the initial septic type of count was changed by treatment in three instances to a nonseptic type and in two to less severe septic counts. One patient has been discharged as clinically improved

in whom the total white cell count is slightly above the accepted normal total but in whom the differential has shown a tendency to stabilize in the hyperplastic zone. Six patients have been discharged with the classification of improved clinically but have found it necessary to continue to cure at home. These 6 cases all showed septic types of blood count throughout the course of the artificial-pneumothorax treatment. Two of them have shown a tendency to stabilize into the hyperplastic type of differential count, but the totals remained elevated in each instance. Five cases in group FA-3 have been subjected to thoracoplasty. This major procedure has resulted in a clinical arrest in three instances, improvement in one and no improvement in the fifth. Two of the three thoracoplasty cases characterized as arrested show definite changes from a markedly septic to a less septic type of blood count. The third case shows a continual elevation of the total count above normal limits, but the differential count has, on repeated checking, shown a hyperplastic tendency. This patient (J. M.) is clinically in excellent condition. The thoracoplasty case classified as improved on discharge continues to cure at home and shows extensive signs throughout the contralateral lung; the blood count is septic in type and it is felt that the disease in the contralateral lung influences this picture. The thoracoplasty case classified as unimproved maintains a septic type of blood count and is continuing to cure. Of the eleven cases who were unsuccessfully treated with artificial pneumothorax and who subsequently died there was in all instances, throughout the illness, an unbroken series of blood counts of the septic type. Of particular interest in these fatal cases is the differential, which as a rule shows high polymorphonuclear and mononuclear cell counts and a subsequent lowering of the lymphocyte ratio.

DISCUSSION

Data are presented in 52 cases of far-advanced pulmonary tuberculosis treated with artificial pneumothorax supplemented in some instances with other methods of collapse therapy and in which the collapsed lungs subsequently reëxpanded. The clinical course of the patient is contrasted in each individual case with a series of blood studies interpreted according to the schema of Medlar.

Twenty-five of these 52 cases were classified as clinically arrested on discharge: in 9 instances the initial septic type of blood-picture changed to a nonseptic type; in two instances a hyperplastic type of blood-picture was assumed; in 10 instances the blood-picture showed a persistent septic

type which, however, became less septic under treatment. One patient discharged as clinically arrested maintained an elevated septic type of blood count throughout the period of observation although the clinical state was strikingly improved. This case subsequently had a relapse and was obliged to resume curing. In 3 cases which presented the septic type of blood count persistently in contrast to marked clinical and roentgenological improvement it was felt that factors other than tuberculosis might possibly be influencing the blood-picture. The following table illustrates the changes found in the blood-pictures of the 25 cases discharged as clinically arrested:

TYPE ASSUMED	NUMBER OF CASES	PER CENT OF CASES
Nonseptic	9	36
Hyperplastic	2	8
Less septic	10	40
Persistently septic (relapsed)	1	4
Extraneously septic	3	12

Thus, 11 cases, or 44 per cent, assumed favorable blood-pictures under treatment. An additional 10 cases, or 40 per cent, assumed blood-pictures that were less septic and therefore more favorable. Six cases were discharged as clinically improved with the blood-picture in agreement with their progress,—in three the initial septic count changed to a hyperplastic type and the patients were able to resume work following reëxpansion of the collapsed lung; the remaining three cases which were of the fibrocaseous type improved clinically under the treatment but are at present obliged to continue curing at home. All of the latter 3 patients continued to have a septic type of count throughout the course of their treatment, but to a lesser degree than that of the initial examination. Ten cases are classified as unimproved,—all of them maintain a septic type of blood picture and, clinically, are stationary or retrogressing. Eleven cases died following the unsuccessful course of artificial-pneumothorax therapy. These fatal cases as a rule presented septic type of counts of increasing severity, especially in the terminal stages.

In several instances where there were chronic infections together with the tuberculosis, the blood-picture was found to be septic in type, and it was thought that the intercurrent infection rather than tuberculosis was the cause of the persistent septic blood-picture, inasmuch as the patients were able to resume work and have remained relatively asymptomatic since discharge.

The importance of the septic type of differential counts in conjunction with normal total counts has been pointed out by previous investigators and is confirmed by our experience. Some individual counts have not remained rigidly within the upper limits of normal as outlined by Medlar. However, for purposes of classification we have identified the trend of the blood-picture as definitely less septic in these instances.

It was found that the pleural effusion complicating the active treatment of cases of pneumothorax does not materially alter the blood-picture. Patients would experience rather severe "fluid reactions" without any deviation from the trend of the blood-picture established previous to the onset of the acute reaction to the fluid. This failure of the blood-picture to respond to an outpouring of pleural fluid was also observed in cases of reëxpanding lung developing fluid incident to the markedly negative intrathoracic pressures experienced during reëxpansion. The latter patients would be asymptomatic, have no knowledge that fluid was accumulating, and be quite surprised to be told on X-ray or physical examination that fluid was present. The blood-picture in these instances showed no change from the hyperplastic or the nonseptic type previously found.

CONCLUSION

The Medlar interpretation of blood counts in cases of far-advanced pulmonary tuberculosis subjected to collapse therapy is a valuable guide in the clinical administration and control of these patients.

Note. I desire to express my appreciation of the coöperation of Miss Fern Och, William Wirt Winchester Hospital, West Haven, Connecticut, in assisting materially this study. The helpful criticisms of Dr. W. B. Soper, New Haven, Connecticut, and Dr. E. M. Medlar, Mt. McGregor, New York, are gratefully acknowledged.

ALTERNATE ARTIFICIAL PNEUMOTHORAX[1]

JEROME HEAD

Not infrequently in the course of treatment by unilateral or bilateral artificial pneumothorax one has occasion to allow one lung to reëxpand, and to initiate or continue collapse of the other. When this becomes necessary before healing has occurred one might naturally feel that not only would the whole collapsing effect of the original pneumothorax be lost, but that, since this lung has now to assume the whole burden of respiration, it would become rapidly worse. A careful consideration of the mechanical factors concerned indicates that neither of these fears are wholly warranted. Clinical results give definite support to the theoretical conclusions.

It is well known that when a tuberculous lung is collapsed the diseased portions, because of their lessened elasticity, contract first, and, when the refills are discontinued, expand last. Before the diseased portion reëxpands a relatively high negative pressure must develop in the pleural cavity. If, as the lung reëxpands, artificial pneumothorax is started or continued on the opposite side, a condition is produced in which the pressure in one pleural cavity is abnormally low, and in the other abnormally high. If the mediastinum is not fixed, this discrepancy in intrapleural pressures produces a shift of this partition toward the side which is reëxpanding, with the result that the well lung there comes to fill the entire pleural cavity without appreciable reëxpansion of the portions that are diseased. If the collapse on the opposite side be kept selective we have theoretically and practically a pneumothorax collapse of the diseased portions of both lungs, respiration being carried on by the portions of both which are unaffected.

In one of the two cases here reported this form of treatment has been carried to successful conclusion. In the other there is every prospect that it will be. In both the disease in the abandoned lung was progressing before it was collapsed. In both the collapse was maintained only for a brief period, two months in one, five months in the other. In both, cavities closed by the pneumothorax remained closed after the pneu-

[1] From Edward Sanatorium, Naperville, Illinois.

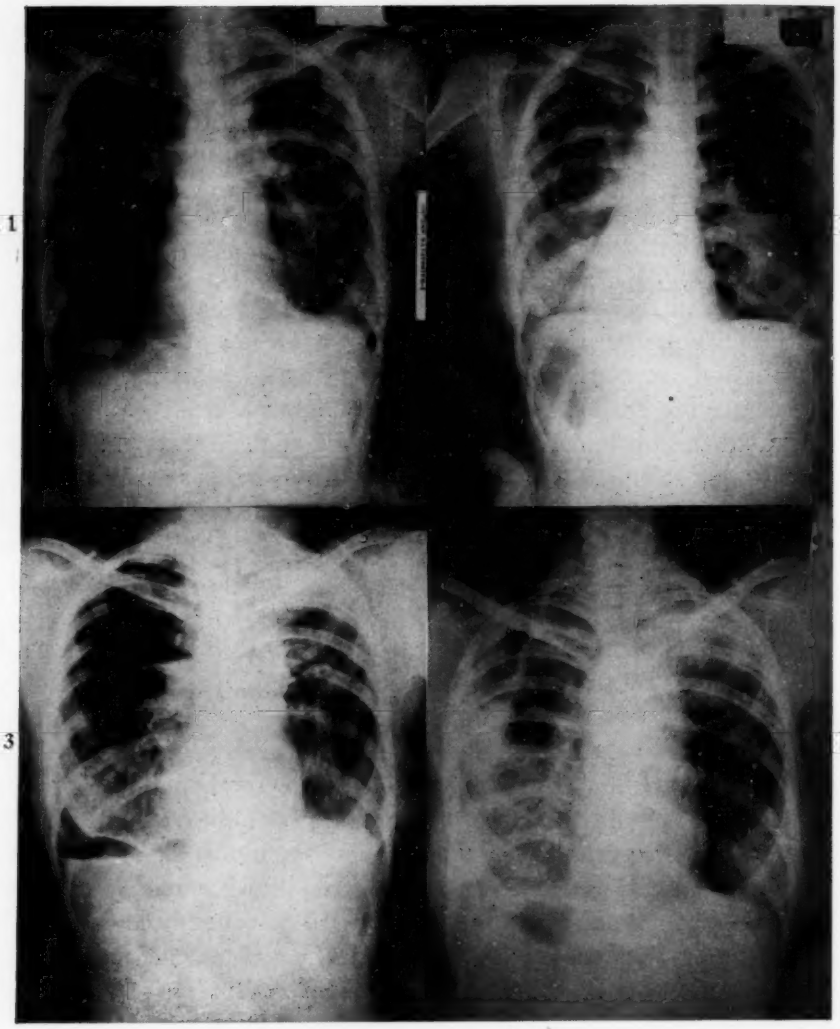

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 1. CASE 1. X-RAY 1. MRS. T. G. DECEMBER 11, 1931

Rapidly advancing caseopneumonic tuberculosis of both lungs, with a large cavity in each midlung field.

FIG. 2. CASE 1. X-RAY 2. MRS. T. G. FEBRUARY 6, 1932

Bilateral artificial pneumothorax has been instituted. In spite of this the cavity in the left lung continued to increase in size. The patient was growing worse.

FIG. 3. CASE 1. X-RAY 3. MRS. T. G. JULY 9, 1932

The pneumothorax on the right has been discontinued and this lung has remained closed. In spite of the fact that the pressure on the left is negative there is a large mediastinal hernia toward the right. The cavity in the left lung is closing rapidly.

FIG. 4. CASE 1. X-RAY 4. MRS. T. G.

Pneumothorax has been discontinued on the left for 4 months. The sputum has remained negative. There is still a small amount of fluid at the apex of the right pleural cavity.

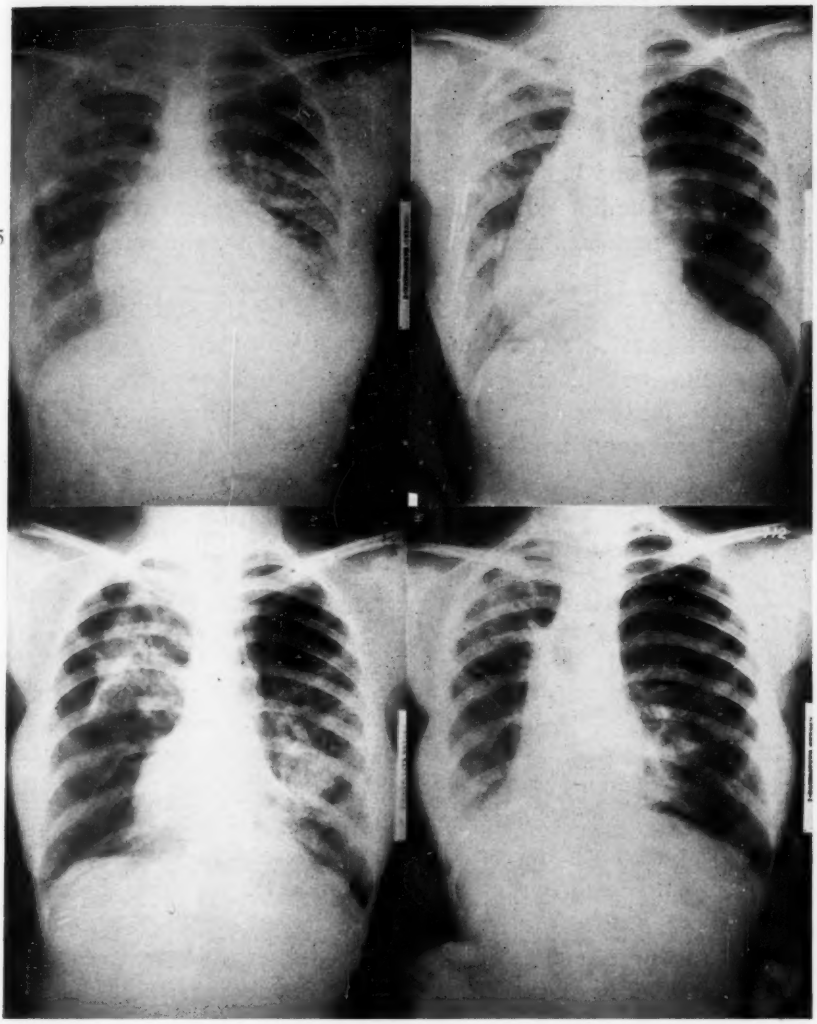

FIG. 5

FIG. 6

FIG. 7

FIG. 8

FIG. 5. CASE 2. X-RAY 1. MISS H. B. JANUARY 6, 1932

The condition at the time pneumothorax was started on the right. Pneumonic tuberculosis of the right lower lobe, caseopneumonic involvement of the left upper lobe. The patient was running a high fever and was failing rapidly.

FIG. 6. CASE 2. X-RAY 2. MISS H. B. JANUARY 10, 1933

Pneumothorax has been maintained on the right for 6 months. Not only is there marked improvement of this lung but most of the exudate on the left has disappeared. There are still multiple cavities in the left upper lobe. At this time the patient was in excellent condition.

FIG. 7. CASE 2. X-RAY 3. MISS H. B. MARCH 6, 1933

Bilateral artificial pneumothorax has been established. There is still a great deal of tuberculosis in both lungs. Shortly after this there developed an acute pleurisy on the left and the disease in the right lung extended.

FIG. 8. CASE 2. X-RAY 4. MISS H. B. JULY 17, 1933

The left lung has been allowed to reëxpand after having been collapsed 5 months. The cavities are closed and the parenchymal lesion quiescent. The mediastinum has moved markedly toward the left. The patient is in excellent condition. Recovery, while far from certain, is possible.

mothorax was discontinued. In both the mediastinum shifted markedly toward the reëxpanding side, so that although the pressure in the opposite pleural cavity remained negative there occurred a definite mediastinal hernia.

As would be expected, and as is evidenced by the case in which the pneumothorax has been terminated, reëxpansion of the lung maintained in collapse may be difficult. Because of the shift of the mediastinum the pleural cavity on this side is larger than normal. Although it is probable that the mediastinum will return toward the midline, phrenicectomy is certainly indicated to facilitate reëxpansion.

I believe that the cases can be best understood by a presentation of their serial roentgenograms.

CONCLUSIONS

1. If artificial pneumothorax is abandoned on one side and started or continued on the other, the marked difference between the pressures in the two pleural cavities, which develops as the air is absorbed, occasions a shifting of the mediastinum toward the abandoned lung, with the result that the sound portions of it can reëxpand to fill the space without appreciable reëxpansion of those portions affected by the disease.

2. If the pneumothorax on the side continued in collapse be kept selective, no increased burden is thrown upon the affected areas in the opposite lung.

3. Two cases are reported in which this sequence of treatment either has been or is being carried to a successful conclusion.

AN EFFICIENT APPARATUS AND TECHNIQUE FOR ARTIFICIAL-PNEUMOTHORAX REFILLS

DEAN H. MINNIS[1]

Within the past two years the number of patients undergoing artificial-pneumothorax treatment at Sunny Acres Sanatorium has increased tremendously. Because of the large number of refills, it was necessary to devise new methods to cope with the situation. The method developed and used at present, consists of a new type of apparatus and a more efficient method of handling the patients.

DESCRIPTION OF APPARATUS

The apparatus consists primarily of a pressure-vacuum pump obtained from a scientific supply-house. The pump, which has a capacity of 700 cc. of air, is mounted on abase with a manometer and an extension arm, as shown in the illustration (figure 1). The extension arm is hinged. Its object is to place the control-valve out in front, in an easily accessible position. Two rubber tubes, extending up the arm and terminating at the control-valve, lead to the pump outlet and to the manometer respectively. A glass tube containing cotton is located on the outlet tube to filter the air. The manometer has only one arm in view; the other extends up back of the panel. This arrangement makes the manometer simpler to read. The piston rod is then calibrated in 100 cc. units. In assembling the pump, it will probably be necessary to soften and grease the leather flaps on the piston to prevent leakage around the piston, and to ensure smooth operation with a minimum of friction.

The piston is exactly counterbalanced by the use of a pulley and counter-weight. Doughnut-shaped weights are placed upon the handle to give the desired pressure. It is possible, however, to use the apparatus without the counterbalance appliance, but in this case the pressure remains constant.

The inlet check-valve incorporated in the pump is usually adequate, but it may be necessary to add another valve. On the apparatus illustrated there is a mercury check-valve.

[1] Sunny Acres Sanatorium, Warrensville, Ohio.

The size of the apparatus is as follows: base, 6 x 4½ inches; height over all, 24 inches. The weights and counterbalance are easily detached, and the machine could be placed in a carrying case if desired.

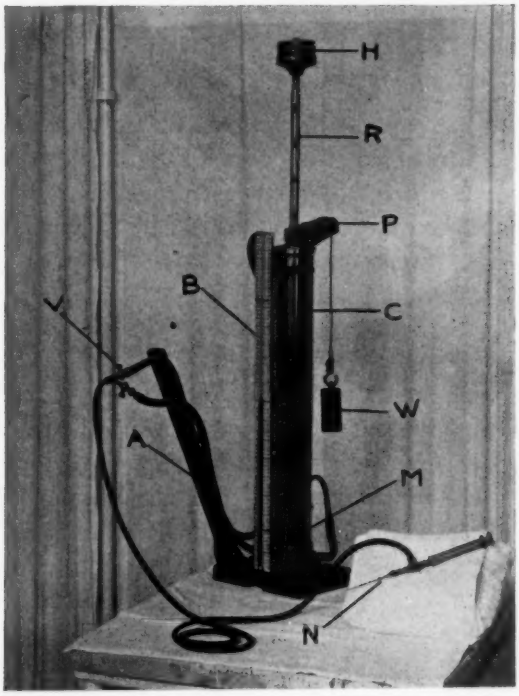

FIG. 1. APPARATUS WITH PISTON ROD PARTLY RAISED

A. Extension arm
B. Manometer
V. Control valve
H. Handle and weights
R. Piston rod
P. Pulley
C. Pump cylinder
W. Counter-weight
M. Mercury inlet check-valve
N. Needle unit

Method of Operation

The control valve, the metal handle, and weights are sterilized, and then attached to the apparatus. The handle screws on easily, and the valve is easily mounted by grasping the rubber tubing with a sterile

towel and inserting the ends of the valve. [*Note:* the valve was made by cutting down an old Floyd-Robinson needle.] The light rubber tubing leading from the valve is also sterilized and attached to the valve-tip. The apparatus is now ready for operation, and, since all of the parts necessary for the operator to touch are sterile and easily accessible, it is therefore possible to operate the apparatus without breaking aseptic technique. The handle is now raised to its fullest extent. Any desired pressure is obtained by placing weights upon the handle. After connecting the tubing with the three-way valve, needle, and syringe, the needle is inserted. After a satisfactory manometric fluctuation, the amount of air introduced is regulated by the control valve. The manometer is connected at all times, if desired.

For initial pneumothorax cases, and for cases in which the intrapleural space is small, no weights are used, and air is sucked in by the negative pressure. This is very graphic, because a small amount of air sucked from the apparatus will cause a noticeable drop in the piston rod.

Advantages

1. The apparatus may be operated by the physician without breaking aseptic technique, thus leaving the nurse free to prepare the patients. This ensures more rapid and efficient operation.
2. The pressure delivered may be varied at will at any time during the operation. The pressure depends upon the amount of weight used and remains constant for any given weight throughout the full course of the piston. This makes it very efficient in positive pressure cases.
3. The air-chamber is refilled by simply lifting the handle of the piston. This requires only several seconds and it may be refilled, if necessary, while the needle is still in the thoracic cavity.
4. The amount of air entering the thorax, even to a very small amount, is seen easily by watching the descent of the piston rod.
5. The manometer is tall, thus preventing ejection or aspiration of the fluid. It may be read from any angle in front of the apparatus.
6. The apparatus is simple to operate, and air may be injected as rapidly or as slowly as desired.

Method of Handling Patients

The set-up is shown in diagram 1. Two tables are placed side by side for the patients. Between these is a space for the operator and a small

table for the apparatus, needles, etc. A patient is employed to do the charting.

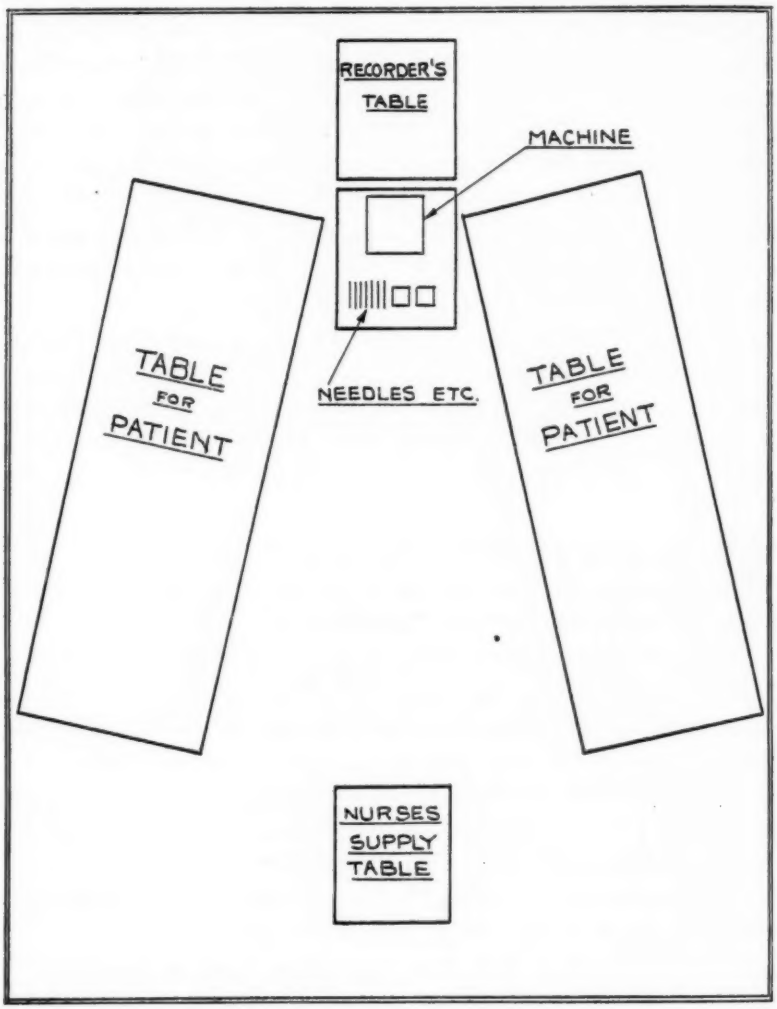

DIAGRAM 1

The two tables are used to avoid waiting. While one patient is being given a refill, another is being prepared and *vice versa*. Only one nurse is necessary for this set-up, and she has adequate time to care for each patient well.

SUNNY ACRES
CLEVELAND TUBERCULOSIS SANATORIUM
PNEUMOTHORAX RECORD

No. 10,993

NAME WARNER, MARGARET AGE 24 ADMITTED 4-10-31

TREATMENT BEGUN AT SUNNY ACRES DATE 6-22-32 SIDE TREATED LEFT

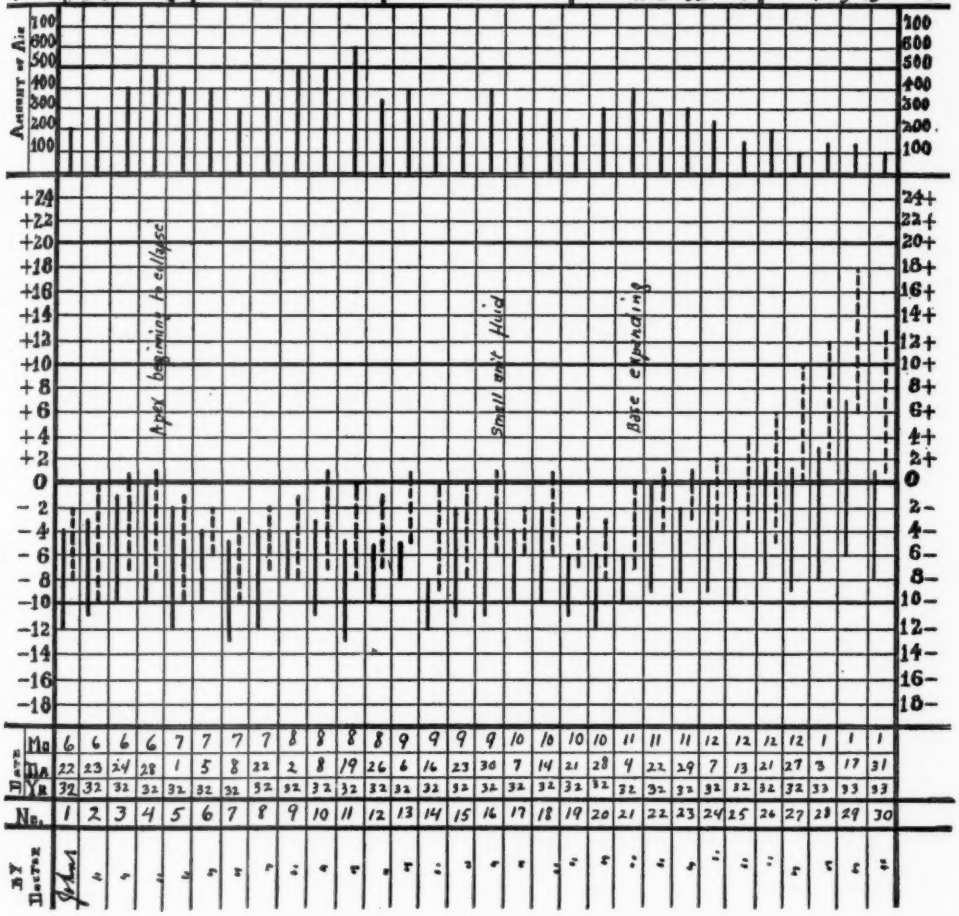

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CHART 1

A Graphic Pneumothorax Record[2]

Each vertical space represents one treatment. The amount of air given is charted just below the fluoroscopic charts, and the pressure below this. The pressure before a refill is charted with an unbroken line, and the pressure afterward with a broken line. Any special notations may be written in.

This chart is graphic and has this advantage: the physician giving a refill can obtain, by merely glancing at the chart, a comprehensive idea of previous pressures and amounts of air more rapidly than from a chart filled with many numerals.

The chart illustrated is that of a case which developed fluid and reëxpanded, in spite of positive pressures. The general trend of the pressures and their relationship to the amounts of air given is well illustrated.

CONCLUSIONS

The technique and apparatus described have markedly reduced the time necessary for routine refills. The time required for each refill varies, of course, with the difficulties encountered in each individual case. But for an average uncomplicated case, it takes two minutes or less. We have given as many as twenty refills within one-half hour by using this new technique, without sacrificing any of the desirable elements. We have four apparatuses of this type now in operation, the oldest having been in continuous use for over eight months. We feel that the technique employed (the use of two tables) and an apparatus simple to operate has proved a satisfactory and efficient method for pneumothorax refills.

[2] The author wishes to express his gratitude to Dr. Joseph Stocklen for his valuable assistance in developing this chart.

THE PARTIAL CAUTERIZATION OF PLEURAL ADHESIONS BY CLOSED INTRAPLEURAL PNEUMOLYSIS[1,2]

JAMES HEDGES FORSEE[3]

Intrapleural pneumolysis is an operative procedure for the severing of adhesions extending between the partially compressed lung and the parietal pleura. The closed method of Jacobaeus, as later modified by Matson, is the operation of choice (1) (2). About 30 per cent of the cases under artificial-pneumothorax therapy have an unsatisfactory pulmonary compression due to pleural adhesions. About one-third of this number are suitable cases for thoracoscopy (1) (2) (3).

It is generally understood that at operation the offending adhesions are completely severed. This is desirable but often impossible and at times unnecessary. The purpose of the operation is to convert an unsatisfactory pulmonary compression into a satisfactory one, that is, one which will bring about a closure of tuberculous cavities by judicious pneumothorax therapy. The partial cauterization of pleural adhesions will often accomplish this purpose.

Pleural adhesions result from a pleuritis. In tuberculosis, their extent is somewhat a measure of the pleural involvement. The extent of the pulmonary involvement, however, is not reflected in the extensiveness of the pleural adhesions (4).

Pleural adhesions consisting of either string-, cord-, small band-, fan-shaped type or types are often the cause of unsatisfactory compression by pneumothorax. Such adhesions may offer comparatively few operative difficulties, while the funnel-, spool-shaped, large band- and diffuse fold-shaped adhesions greatly increase the operative difficulties. The difficulties encountered in funnel- and spool-shaped adhesions are due chiefly to the indistinct blending of the lung and the fibrous tissue of the adhesion. They often contain prolongations of cavities and large blood-vessels. The severance of such adhesions may result in damage to the lung parenchyma, haemorrhage, or opening of cavitation.

[1] From the Surgical and Medical Services, Fitzsimons General Hospital. Read before the Denver Sanatorium Association, Denver, Colorado, April 25, 1933.

[2] Published by permission of the Surgeon-General, U. S. Army.

[3] Captain, Medical Corps, U. S. Army.

Large band- and diffuse fold-shaped adhesions present all of the above difficulties and in addition the serious technical handicap of being unable to visualize their entire circumference on thoracoscopy. These adhesions result from an interlobar pleuritis which extends to the parietal pleura or certainly from a more generalized pleuritis. Following the institution of pneumothorax therapy, the lung is partially compressed and the adhesions take on a curtain-like appearance. They are usually situated in the costovertebral gutter, at the site of the interlobar fissure or in the apical area, and the lung often remains close to the thoracic wall with extensions from the main adhesion radiating in all directions. It is in these types of adhesions that incomplete cauterization is often of great benefit.

SELECTION OF CASES

All cases of pulmonary tuberculosis under artificial-pneumothorax therapy with an unsatisfactory pulmonary compression due to adhesions, which after three to four months' treatment do not show a decrease in the quantity of tubercle-bacilli-laden sputum and a decrease in the size of the cavity, are potential cases for intrapleural pneumolysis. Meticulous study of serial roentgenograms before and during the course of the pneumothorax treatment is a prerequisite to thoracoscopy. Roentgenographic study alone cannot determine the number, width or thickness of the adhesions. It is not possible roentgenologically to determine whether the edges or the entire width of the adhesion is shown. The anterior border of a wide band- or fold-adhesion may appear as other distinct cords giving the impression of multiple, small cord-adhesions. In other instances, only the anterior border may be of sufficient density to show, yet the adhesion be rather wide. Often many small adhesions may not be shown on the roentgenogram, while others of greater density may be hidden by bony structures. Roentgenograms are of great value in selecting cases for thoracoscopy; however, the selection of case for actual cauterization is made during thoracoscopy.

Large band-shaped adhesions are often situated laterally between the second and fourth ribs, while large, diffuse, fold-shaped adhesions are generally found in the posterior apical area. These adhesions, especially those located apically, are the most difficult to cauterize. This is due to the fact that the pleural cavity is smallest in this region, the mobility of this portion of the lung is slight with little tension being placed on the adhesions, making the operation, technically, more difficult and increasing

the chances of postoperative complications. The indistinguishable blending of the lung and adhesion in these cases necessitates the differential thoracoscopic determination between the operative procedures of extrapleural thoracoplasty and intrapleural pneumolysis. The literature contains many favorable reports from both procedures and is often characterized by whether or not the author performs the adhesion-cutting operation. Archibald (5) favors complete thoracoplasty; Hedblom (6) is of the same opinion. The former authority performs an open pneumolysis for the severing of pleural adhesions.

Matson (2), an expert phthisiologist and thoracic surgeon, prefers closed intrapleural pneumolysis whenever the adhesions are narrow enough to be successfully severed and reports 70 per cent of unsatisfactory pneumothoraces being converted into satisfactory ones after operation. He states that all sides of the adhesion should be studied before cauterization is attempted, and, in general, we follow Matson's advice. We believe that in cases with partial pneumothorax and obviously a large area of the upper lobe adherent to the thoracic wall and containing a patent cavity, extrapleural thoracoplasty with pack (Casper operation) is the operation of choice (7).

We believe that in cases with an unsatisfactory pulmonary compression due to pleural adhesions, regardless of the location and not obviously presenting a large area of adherent lung, thoracoscopy is indicated. Our experience has shown that, although it may be impossible to completely sever the larger adhesions, partial cauterization with coagulation of their parietal pleural attachment is often followed by the closure of the cavity under continued pneumothorax therapy.[4] Repeated operations may be thought necessary to completely sever the adhesion; however, it may be found that a satisfactory pneumothorax has resulted from a single cauterization, making further operations unnecessary.

Thoracoplasty in the above type of cases offers the following advantages over intrapleural pneumolysis: first, there is no time-loss in continuing a pneumothorax which may not result in the closure of the cavity; second, the complications which may result from a continuance of pneumothorax or intrapleural instrumentation are avoided; third, well-performed thoracoplasty is a more universally obtainable operation than is closed intrapleural pneumolysis.

Closed intrapleural pneumolysis has the following advantages over

[4] This procedure was first suggested to the author by Dr. R. C. Matson, Portland, Oregon.

thoracoplasty: first, it is a much less formidable and mutilating operation, the degree of shock is hardly comparable and uncomplicated, the post-operative course is milder; second, a larger amount of reëxpanded functional lung tissue is available after pneumothorax is discontinued than is the case after the arrest of the disease by thoracoplasty; third, a larger percentage of cavities are closed after a satisfactory pneumothorax is produced than are closed by thoracoplasty; fourth, intrapleural pneumolysis can be successfully performed in cases in which thoracoplasty is contraindicated; fifth, if cauterization does not accomplish the desired result or is followed by complications, thoracoplasty, although probably not as effective, can be performed if other therapeutic measures have failed.

At thoracoscopy, the adhesions found suitable for incomplete cauterization are essentially of two types; first, large, thick, well-organized, band-shaped adhesions situated either laterally or at the apex; second, single or diffuse fold-shaped, apical adhesions.

The operative difficulties encountered in severing such adhesions are greatly increased by the operator's inability to view all surfaces of the structure. Under such circumstances, individualization of cases and accurate orientation and interpretation of the thoracoscopic picture are paramount. At this stage in the operation, it is necessary for the operator to determine, in each case, what procedure he will follow: complete cauterization, incomplete cauterization, coagulation of the parietal pleural attachment alone or some other operative procedure. The following facts are important in arriving at the decision.

The general clinical condition of the patient may preclude other operative procedures and an heroic attempt must be made to save the patient's life. Cauterization may, in such cases, offer the only hope and should be performed if the immediate physical condition permits. The patient may have refused to accept the recommendations for thoracoplasty, pneumothorax combined with phrenic exairesis may have failed to accomplish the desired result, and, again, cauterization may be the only available procedure.

If a large thick, laterally situated, band-shaped adhesion is present with one or more inches between the parietal pleura and the partially compressed lung, cauterization should be done. If the adhesions are very dense and their severing requires considerable time, partial cauterization is preferable. It is necessary to decide early whether or not complete cauterization is to be done, as it is of utmost importance to leave

uncauterized a sufficient amount of adhesion to prevent its subsequent spontaneous rupture. Usually one-fourth to one-half of the width of adhesion can be safely cauterized.

If the adhesion is situated apically and is of a band- or shelf-like structure, presenting one or more inches of distinct adhesion, partial cauterization of one-half to two inches of the adhesion, with coagulation of the parietal pleural attachment, is recommended. If there is less than one inch of free adhesion surface or more than one band present, we believe cauterization should not be attempted but that thoracoplasty be performed at an early date.

If the adhesion is a thin, simple or diffusely folded apical adhesion, with one or more inches between the parietal pleura and compressed lung, we believe partial cauterization to be advisable. Cauterization of as much as four inches of such an adhesion has been carried out with beneficial results. If such adhesions present edges more than 1 to 2 cm. in thickness, with less than one inch between the parietal pleura and lung, we believe thoracoplasty again to be the operation of choice. Such facts cannot be ascertained except by thoracoscopy. The quantity of adhesion to be severed must vary with each case, and, here again, experience and judgment are the operator's safeguards.

The immediate operative dangers associated with closed intrapleural pneumolysis are haemorrhage and damage to the lung parenchyma, both of which are greatest in the type of adhesions in which partial cauterization is indicated.

The postoperative complications encountered in partial cauterization include all of those of closed intrapleural pneumolysis (8). The greatest of these are superimposed spontaneous pneumothorax, either immediate, within seventy-two hours, or delayed several days or weeks. The uncut portion of the adhesion is placed under greater tension, and within its immediate vicinity is an area of devitalized tissues which may extend into the lung. The increased tension may be greater than the uncut adhesion can withstand, especially during a spasm of coughing or increased strain resulting in its rupture with a tearing of the lung. Superimposed spontaneous pneumothorax may result from the rupture of fiddle-string adhesions not visualized at thoracoscopy or inaccessible for cauterization. If the lung is completely collapsed as a result of the superimposed spontaneous pneumothorax the fistulous opening may become closed and a pyopneumothorax prevented. Mixed infection in such cases is a very grave complication, due to the great size of the empyema cavity and its resultant severe toxaemia.

COMPLICATIONS

Since November, 1930, we have performed closed intrapleural pneumolysis on 16 cases. In seven, or 43.7 per cent, the adhesions were suitable only for incomplete cauterization. These, of course, were not the most ideal cases, and complications would be expected to be more frequent and severe. Serous effusion, sufficient to warrant a diagnosis and not present preoperatively, occurred in one case. Superimposed spontaneous pneumothorax occurred in three cases, one, seventy-two hours postoperatively and two days after an air-refill of 600 cc. In another case, the accident occurred eleven days postoperatively following a severe attack of coughing. This was a case of extensive bilateral involvement with bilateral cavitation, and whether or not its immediate cause was the rupture of an adhesion or a subpleural tubercle is debatable. This patient developed a pyopneumothorax with further excavation in the contralateral lung and died five weeks postoperatively. The third case developed a superimposed spontaneous pneumothorax six weeks postoperatively when he suddenly jumped out of bed. There was an increase in the pleural effusion but no permanent ill effects resulted. Thus, in only one of seven cases did an immediate superimposed spontaneous pneumothorax follow operation and then only after an air-refill of 600 cc., a quantity considerably larger than what we now recommend. We have had no tuberculous empyemata, obliterative pneumothoraces, pleurocutaneous fistulae or haemorrhages as complications in this group. Secondary major surgery has not been required in any of these cases.

RESULTS

A satisfactory pneumothorax, with a decrease in the quantity of sputum and in the size of the cavity and with evidence of clinical improvement, has occurred in five, or 71 per cent, of the 7 cases. In the other two cases the complication of a superimposed spontaneous pneumothorax caused an unfavorable result. In one case, two partial cauterizations have been done. Recent roentgenograms show great improvement in the collapse of the large cavity; the time, however, has been insufficient and further operation may be necessary. In another case, a large apical cavity was apparently closed within five months but fourteen months postoperatively there is evidence of a patent cavity on roentgenogram. In no case that we have been able to follow has the lung been allowed to completely reëxpand. In one instance there was only a small amount of

pneumothorax present when the patient abandoned the hospital eight months after operation. All of these cases may be considered technically unsuccessful in that the offending adhesions were not completely severed. However, 71 per cent were clinically successful, as evidenced by the decrease in the quantity of sputum, increased or complete collapse of the cavity and clinical improvement.

CONCLUSIONS

A review of the literature and a critical analysis of 7 cases of partial cauterization of pleural adhesions by closed intrapleural pneumolysis warrants the following conclusions:

1. Incomplete cauterization is most suitable for large band- or diffuse fold-shaped adhesions situated laterally or apically.
2. Thoracoscopy should be performed in all cases in which the above types of adhesions interfere with satisfactory pulmonary compression and further operative procedures determined by the thoracoscopic findings.
3. Satisfactory results were obtained in 71 per cent of the 7 cases treated by partial cauterization.
4. The electrosurgical method is the one of choice in performing partial cauterization.

Case reports

1—E. H.: Age; 29; soldier. Patient admitted to Fitzsimons Hospital in April, 1929, with extensive, confluent, caseofibrous, pulmonary tuberculous involvement above second-rib level, right. On February 2, 1930, artificial pneumothorax, right, induced. On December 31, 1930, thoracoscopy with partial cauterization carried out without complications. Pneumothorax continued without appreciable effect upon the cavity and four months later a second-stage of partial cauterization was done. At this time the adhesion was found to be about 3.5 cm. in width, and about 1 cm. in thickness and approximately three-fourths of the adhesion was severed. The following day the lung expanded considerably and 600 cc. of air was given with a slightly negative intrapleural pressure. Two days later, fluoroscopy showed almost complete collapse of the lung. On the morning of the tenth postoperative day, the patient's condition suddenly became critical, following a violent attack of coughing. A needle was inserted into the pleural space for the relief of pressure. Patient responded well for a few hours but died the following morning. At the autopsy, no patent bronchial fistula was found. The right pleural cavity was full of serous fluid and the heart's blood contained a haemolytic streptococcus.

2—R. C. G.: Age; 26; coal-miner for three and one-half years before enlisting in the Army in 1924. Admitted to Fitzsimons Hospital November 1, 1930, with active bilateral pulmonary tuberculosis and with indefinite cavitation above second-rib level, left. Artificial pneumothorax, left, induced in May, 1931. Thoracoscopy was done August 11, 1931, and five adhesions, varying in size from small cord- to band-shaped adhesions, 3 cm. in width and 0.5 cm. in thickness, extending from the partially collapsed lung to the second-rib level in midaxillary line, were severed. After these were cut, a large band-shaped adhesion extending to the first rib and posteriorly to blend with the adherent lung tissue and parietal pleura was seen. This adhesion was coagulated at all available points about its chest-wall attachment.

The postoperative course was mild and sputum soon became negative. Positive intrapleural pressure was used with production of small amount of fluid, which was absorbed. By February, 1932, the patient had no pulmonary symptoms and the cavity was not seen on lateral or apical roentgenograms. He abandoned the hospital March 15, 1932, and the end-result is unknown.

3—D. P. L.: Age; 22; soldier. This patient entered Fitzsimons Hospital June 5, 1930, with extensive bilateral pulmonary tuberculous involvement and cavitation. Artificial pneumothorax, left, induced October 21, 1930. At thoracoscopy, July 13, 1931, a large band-shaped adhesion was found extending from the second rib, posterior axillary line, into the first intercostal space and apex. A cord-shaped adhesion, size of one's fifth finger, was seen in the second intercostal space, posterior axillary line, which was coagulated at its parietal pleural attachment. The band adhesion was coagulated and cauterized through approximately three-fourths of its chest-wall attachment. Several small tubercles were seen on the parietal pleura close to the adhesions. The postoperative

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FIG. 1. Case 4. C. L. C. Large band-shaped adhesion holding open large cavity in upper lobe, right. Roentgenogram taken day of first partial cauterization and after four months of artificial pneumothorax treatment.

FIG. 2. Case 4. C. L. C. Five months after second partial cauterization. Cavity markedly reduced in size and it is believed that it will close by continuance of pneumothorax treatment.

FIG. 3. Case 6. C. F. G. Large apical cavity held open by numerous adhesions. Roentgenogram taken after nearly four months' artificial pneumothorax treatment and three days prior to partial cauterization.

FIG. 4. Case 6. C. F. G. Six weeks after partial cauterization. Cavity indistinctly seen. Eight months after operation patient discontinued pneumothorax treatment and left the hospital against medical advice but clinical improvement has continued.

FIG. 5. Case 7. E. N. S. Large diffuse fold-shaped adhesion preventing closure of cavity, right. Roentgenogram taken after four months' pneumothorax treatment and six days prior to partial cauterization.

FIG. 6 (retouched). Case 7. E. N. S. Nine months after partial cauterization. Cavity closed, pneumothorax treatments being continued and patient steadily improving.

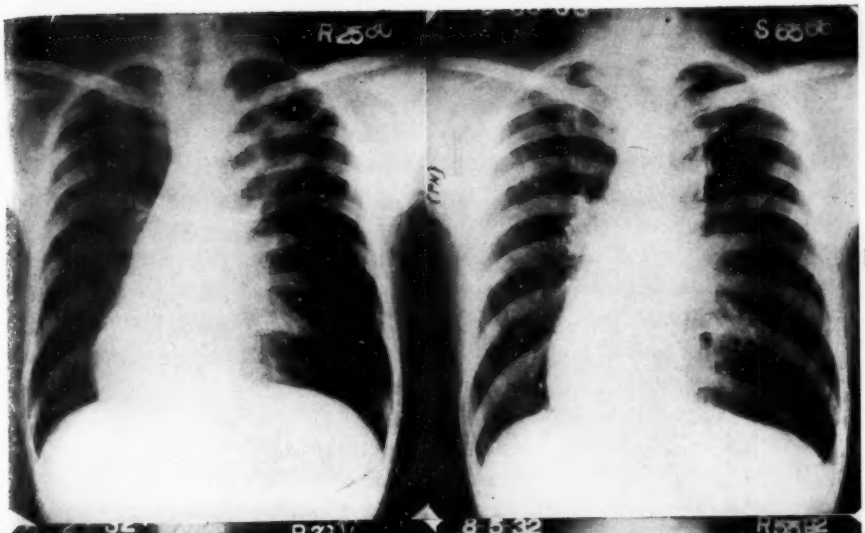

Fig. 1

Fig. 2

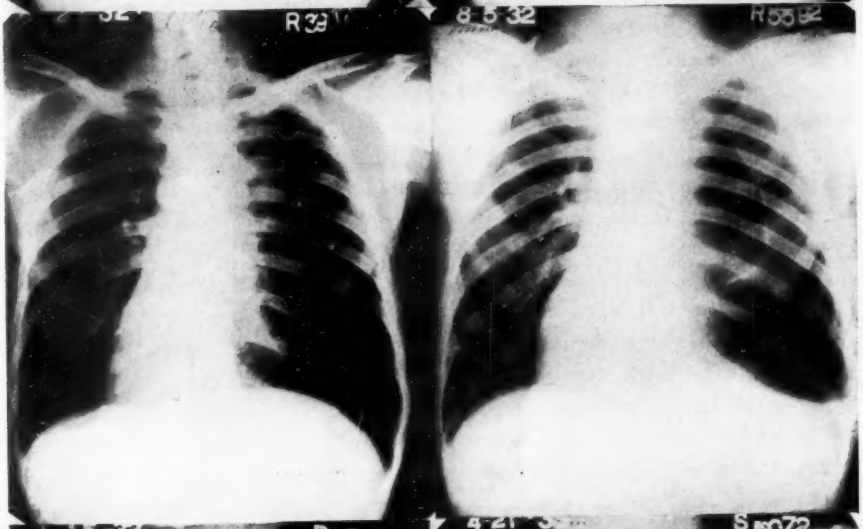

Fig. 3

Fig. 4

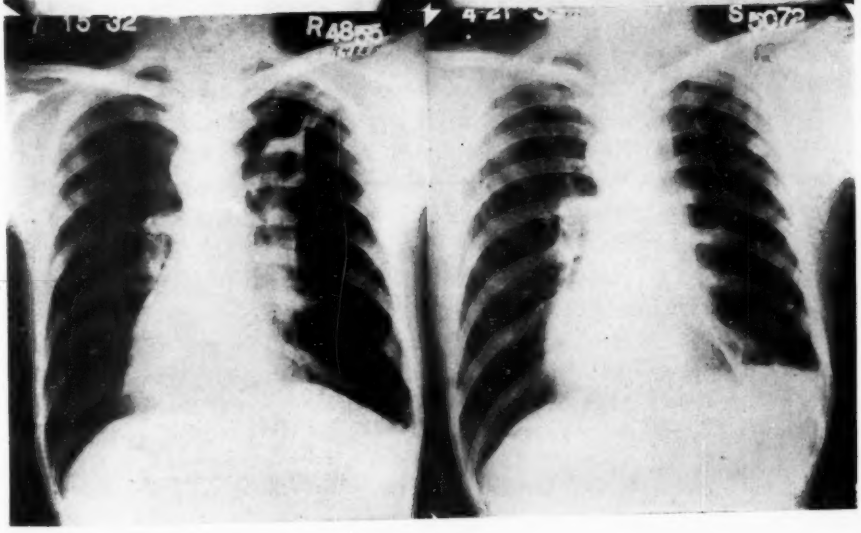

Fig. 5

Fig. 6

course for the first eleven days was uneventful. On the night of eleventh postoperative day, patient had violent coughing attack followed by dyspnoea and tightness in the left chest. Roentgenograms showed complete pulmonary collapse. Removal of air at frequent intervals was required, a hydrothorax developed which became a pyothorax, cavities in the contralateral lung increased, and patient died August 26, 1931, six weeks after operation. Autopsy failed to show a patent bronchial fistula which was clinically present.

4—C. L. C.: Age; 31; soldier. Admitted to Fitzsimons Hospital December 18, 1925, with a 3-cm. thick-walled tuberculous cavity at level of second rib, right, anteriorly. Artificial pneumothorax, right, induced January 8, 1926, and continued until July, 1926, at which time patient discontinued treatment against medical advice. He reëntered Fitzsimons Hospital in December, 1931, with a 4- by 5.5-cm. cavity in the right upper lobe. Artificial pneumothorax, right, induced January 19, 1932. Five inches of the right phrenic nerve removed nine weeks later with no appreciable rise of the diaphragm. At thoracoscopy, May 17, 1932, (figure 1), a thick fold-shaped adhesion situated along the third rib and second intercostal space in midaxillary line, extending posteriorly to become blended with the adherent lung was seen. Approximately 1 cm. of the free edge of this adhesion was cauterized. No pleural tubercles were seen and no haemorrhage occurred. The postoperative course was uneventful. On January 27, 1933, thoracoscopy with cauterization of 2 cm. of the free edge of the adhesion was carried out with the coagulation of a narrow zone of the parietal pleural attachment. Postoperative course again uneventful. Since operation, he has gained 6 pounds, has slight sputum (positive), and small pleural effusion has been absorbed. Recent roentgenogram shows cavity considerably smaller and it is believed the cavity will close by continuance of pneumothorax (figure 2).

5—C. M. B.: Age; 42; soldier. Patient admitted to Fitzsimons Hospital September, 1931, with multiple pulmonary tuberculous cavitation above the second-rib level, right, and an ulcerative laryngitis. Artificial pneumothorax, right, was induced October 13, 1931. At thoracoscopy, February 18, 1932, one cord-adhesion, 1 cm. in diameter, extending to third-rib midaxillary line, was severed. A large band-shaped adhesion extending from 2nd intercostal space in posterior axillary line into the apex blended with the adherent lung. This adhesion was coagulated and severed to the point at which it became blended with the adherent lung posteriorly; approximately one inch of the free edge of the adhesion was severed. Until January, 1933, patient was semiambulant, temperature was normal, had no sputum, and had gained 18 pounds. At this time, symptoms of fatigue and productive expectoration appeared and roentgenograms showed a 1.5-cm. cavity in contralateral lung and cavitation on the

right, patent. Patient would not consent to pneumothorax, left, and bed-rest has resulted in moderate improvement. Ultimate prognosis, however, is less favorable.

6—C. F. G.: Age; 34; barber. Diagnosed active pulmonary tuberculosis at Fitzsimons Hospital in February, 1932, with a 5- by 7-cm. cavity in the right apical area. Artificial pneumothorax, right, induced March 1, 1932, and phrenic exairesis, right, done March 17, 1932. At thoracoscopy, June 24, 1932, (figure 3), a diffusely fold-shaped adhesion was seen extending from the partially compressed lung to the second rib and interspace in the mid- and posterior axillary line. The adhesion was folded upon itself in such a manner that it appeared to be a distinct band, measuring approximately 5 cm. in length and 0.5 cm. in thickness. This adhesion was coagulated and cauterized down to the blended pulmonary tissue. A second and third band-shaped adhesion could then be seen and were a part of the diffusely folded adhesion. They were treated in a similar manner. Approximately 10 cm. of adhesion surface close to the parietal pleura was severed. The pulmonary compression was immediately increased (figure 4 retouched) and continued until patient left the hospital against medical advice February 18, 1933. A communication in July, 1933, stated that he discontinued pneumothorax treatment after leaving the hospital but clinical improvement had continued.

7—E. N. S.: Age; 41; army officer. Diagnosed active pulmonary tuberculosis in October, 1931, with multilocular cavitation behind second rib, right. Artificial pneumothorax induced March 15, 1932. At thoracoscopy, performed July 21, 1932 (figure 5), a thin diffuse, fold-shaped adhesion indistinctly blended with adherent lung was found extending from the partially compressed lung to the second rib and intercostal space in the posterior axillary line. Approximately 4 inches of adhesion was severed. A thin, band-shaped adhesion situated in the costovertebral gutter at the fourth-rib level was then seen which was coagulated and severed down to the blended lung tissue. Postoperative course was uneventful. On September 2, 1932, the patient suddenly jumped out of bed and experienced a sudden sharp pain in the right upper chest. Fluoroscopy four days later showed the cavity much reduced in size with increase in pulmonary compression of the upper lobe. Moderate pleural effusion developed which has been gradually absorbed. In June, 1933, he had no cough or sputum, presented general clinical improvement and at the present time receives a pneumothorax refill every two to three weeks (figure 6 retouched).

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ATELECTASIS AND THE DISAPPEARANCE OF CAVITIES[1]

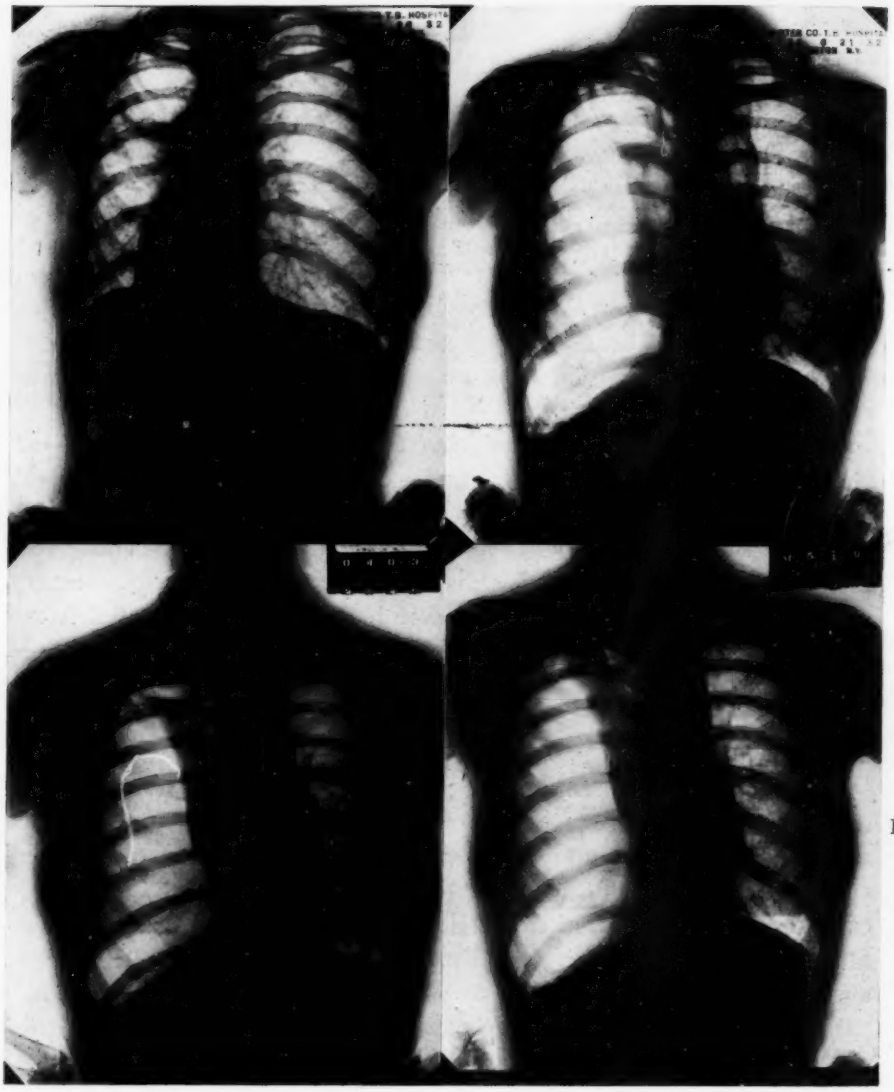
F. W. HOLCOMB AND G. W. WEBER

A recent paper by Dr. Pol N. Coryllos on *The Importance of Atelectasis*, which appeared in the July (1933) issue of THE AMERICAN REVIEW OF TUBERCULOSIS, brings new light on certain facts which so far have remained almost unexplained.

His theory of atelectasis producing the disappearance of cavities is very ingenious, and he has shown with X-rays how large cavities, of long standing, may sometimes disappear from the picture, often in a relatively short time, without any particular treatment being done for them. In his paper Dr. Coryllos has dealt mostly with the disappearance of cavities for which no collapse therapy had been attempted, but from his studies he concludes that the closure of cavities in many cases of collapse therapy is probably due to the fact that they become atelectatic because the bronchi leading to them have become in some way or another occluded.

It is our purpose in this paper to try to corroborate Dr. Coryllos's explanations concerning some cases in which pneumothorax treatment sometimes gives very startling results. They are usually cases with apical cavities partially adherent to the chest-wall, or with marginal cavities which are resistant to pressure apparently because of their dense fibrotic border, or in which a great pressure cannot be exerted because of a weak mediastinum, and, while the pneumothorax succeeds in collapsing the rest of the lung, it appears to have very little if any action on the cavity itself. Highly positive pressures, frequency of refills, and increase in the amount of air are usually of no avail, and in most cases the only result is to give discomfort to the patient. The cavity remains open for months, the sputum is persistently positive, and although the general condition of the patient may have greatly improved, we feel that the prognosis of the case is unfavorable so far as closure of the cavity and danger of infection in the contralateral lung are concerned, and we may begin considering some other form of surgical collapse. This condition may go on for months, and then, unexpectedly, in a few weeks, the

[1] From the Ulster County Tuberculosis Hospital, Kingston, New York.



CASE 1

FIG. 1. Case 1. First X-ray January 26, 1932. End-result of caseous pneumonic process in left upper lobe. General condition very poor. Sputum loaded with tubercle bacilli.

FIG. 2. Case 1. X-ray June 21, 1932. Pneumothorax instituted February 26, 1932, and carried on with regular refills and final pressures of 0 and plus 2. Condition improved but sputum still positive.

FIG. 3. Case 1. X-ray November 11, 1932. Cavity still present. Sputum negative. Regular weekly pneumothorax refills with final pressures of plus 1 and plus 4.

FIG. 4. Case 1. X-ray January 16, 1933. Disappearance of the cavity. Sputum and gastric contents negative for bacilli. Pneumothorax refills every ten days with final pressures of 0 and plus 2.

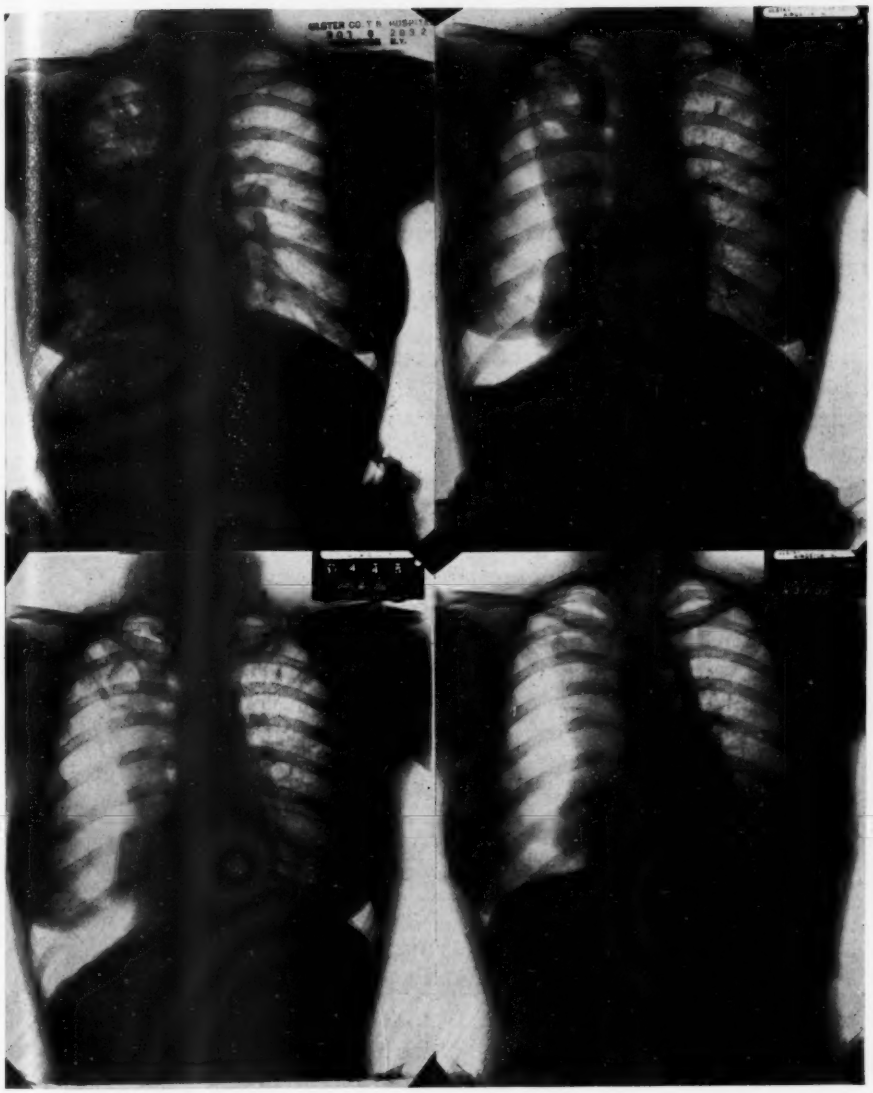


Fig. 5

Fig. 6

Fig. 7

Fig. 8

CASE 2

FIG. 5. Case 2. X-ray June 23, 1932. Caseous pneumonic process in left lung. Large excavation in infraclavicular region.

FIG. 6. Case 2. X-ray September 17, 1932. Pneumothorax had been induced July 8, 1932, and carried on with regular refills. Final pressures 0 and plus 4. Cavity still present. Sputum positive with large number of bacilli in each field.

FIG. 7. Case 2. X-ray December 6, 1932. Pneumothorax unsuccessful. Cavity in upper lobe still evident. Weekly refills with final pressures 0 and plus 4. Sputum positive for tubercle bacilli. (Gaffky V.)

FIG. 8. Case 2. X-ray March 1, 1933. Disappearance of cavity in left upper lobe. Sputum and gastric contents negative for tubercle bacilli. Pneumothorax with weekly refills and final pressures of 0 and plus 4.

sputum becomes negative, and, on taking an X-ray, we find that the cavity has disappeared and that the pneumothorax, which up to this time has been unsatisfactory, has become successful. It has been our experience that this happens indifferently either with positive manometric pressures or with pressures around zero. In one case a shifting mediastinum prevented positive pressures at all. We report here the two following cases which, we think, may illustrate sufficiently our point.

In the first case with the end-result of a caseous pneumonic process in the left upper lobe, pneumothorax was instituted in February, 1932, and regular refills were given from three to seven days apart with initial negative pressures and final pressures averaging plus 2, and 0. The condition of the patient improved greatly. Nevertheless, the cavity in the upper lobe persisted almost unchanged until December, 1932, while the rest of the lung had been collapsed at the beginning of the treatment. An attempt to force further collapse with an increased amount of air and of pressure was unsuccessful because of the shifting mediastinum, which gave discomfort to the patient. To our surprise, the sputum which had been constantly positive for all that period, became negative for the first time in October, 1932. But this fact failed to modify our prognosis, because the cavity was still existent and unchanged in November. However, at the beginning of January, when another X-ray was taken, it had completely disappeared and in its place the area appeared to be atelectatic. So far, not only the sputum has been constantly negative, but also the gastric contents have been negative for tubercle bacilli.

The history of the second case is similar. Pneumothorax of the left side was started in July, 1932, and was carried on with regular refills and the final pressures were kept on an average of 0, and plus 4. The general condition of the patient improved greatly; she gained weight and her cough subsided, but her sputum, although greatly decreased, remained positive. An X-ray of January 23, 1933, showed a complete collapse of the left lung with the exception of the cavity in the upper lobe. A physical examination at that time showed complete absence of breath-sounds all over the left lung, while only one month previously there were definite signs of a large cavity. At the beginning of February the sputum became negative for the first time, and on March 1 an X-ray showed the disappearance of the cavity. Up to date, with refills every two or three weeks, with very small amounts of air, and with negative final pressures, the situation in both patients has remained the same, although the lungs have been slowly reëxpanding. It is worth while to note that in both cases the first idea of a radical improvement was given us by the negative sputum, and in one case by the absence of physical signs, which preceded by a few weeks the disappearance of the cavity. There seems to be very little explanation of this phenomenon.

Coryllos, who in several papers has given the results of his extensive studies on the aeration of the lung and on atelectasis, gives an explanation in his last paper, which in our opinion seems to be the right one. He studied the gaseous contents of some cavities by taking direct specimens from them, with the usual needle connected to a pneumothorax machine. He found that some of these cavities have a negative manometric pressure and some a neutral one. Analyzing the specimens of gases taken from them, he found that the cavities with negative pressures seem to have an increase of CO_2 and a decrease of oxygen, and *vice versa*, while the cavities with a neutral pressure seem to have the same gaseous content as the bronchi. From this Coryllos concludes that some cavities have a direct communication with the outside air, while the others appear to be shut off. Therefore he states that

> We may compare an open cavity to a pneumothorax with bronchial fistula, in which although the air is constantly "pumped out" by the circulating blood, it cannot be exhausted because it is continually renewed. On the contrary, a cavity with obstructed bronchial outlet is similar to a closed pneumothorax, in which the air is gradually absorbed even when the pleura presents considerable thickening (1).

For this reason Coryllos believes that in some cases the bronchi become occluded, thus shutting off the cavity from the outside air. When this happens, the air contained in the cavity is gradually absorbed, producing in this way atelectasis and consequently collapse of the cavity.

It is our opinion that certainly some process like this must occur, otherwise it would be difficult to explain why these cavities, which have remained patent for so long a time, resisting the collapse of the pneumothorax, should suddenly disappear without any radical change in the management of the treatment. That their communication with the outside air is shut off before they disappear is proved by the fact that the sputum becomes negative and the physical signs are absent before their disappearance. In other words, before the air they contain is absorbed.

How does this bronchial occlusion take place? There are several ways to be considered: first, occlusion by a caseous plug; second, by kinking or compression of the bronchi; and third, by occlusion by constriction.

An occlusion by plugging with some caseous material seems unlikely to occur, at least in a permanent way. It is true that the communicating bronchi can be plugged by secretion, but this obstruction can never be-

come so complete or so thick as to prevent the passage of air, and it is bound to be removed sooner or later. But the most important objection to that is that if we were to explain the atelectasis of the cavities in our cases by a bronchial plug, this phenomenon should occur earlier, when the cavity is still caseating and sloughing off, and not when the amount of secretion has decreased a great deal.

On the other hand, kinking or occlusion by compression is also very unlikely. Coryllos, in a paper published in the *Journal of the American Medical Association* (2), seems to give great importance to this factor, but we think differently. So far, from the pathological reports, we have no proof that the collapse by pneumothorax can produce a kinking of the bronchi to the point of completely preventing the passage of air through them. Gardner (3), who studied very carefully postmortem 15 cases of pneumothorax of different durations, suggested that "the collapse of the lung produces a kinking of the lymphatic trunks." But he did not report any case of kinked bronchi. However, in another part of his paper he stated that the cartilaginous walls of the larger bronchi prevent compression of these tubes. In fact, there are several arguments against this occurrence. First of all, the compression produced by the pneumothorax, assuming that there is any compression at all, is not permanent. Even if the final readings are highly positive, they remain so only for a few hours (depending on the greater or less permeability of the pleura), to become again gradually neutral if not negative, because of the active pleural gaseous exchanges. To a certain point a kinking or compression may be possible in a thoracoplasty, when perhaps in some cases a stronger and certainly a steadier pressure is exerted. It may be also possible in a hydropneumothorax with a fair amount of fluid. Furthermore, even if we were to assume that a permanent compression could be exerted with the pneumothorax at a positive pressure, which after all represents the weight of only a few cubic centimetres of water, we could only kink and collapse the capillary bronchi or bronchioli leading to the infundibula, but not the lobular and much less the lobar bronchi, because, as Gardner has stated, and as we know from their histology, the bronchi have a fibrous coat and an outer layer of elastic fibres and are lined by cartilaginous platelets down to the twigs of about one millimetre in diameter, and consequently are fairly rigid and not so easily collapsed or kinked. These large cavities, unyielding to the pneumothorax pressure, are not fed by the smaller bronchi, but by the larger ones. Moreover, cavities disappear during pneumothorax without any positive pressure at all being exerted.

If we exclude these two causes, there seems to be only one other way of bronchial obstruction, and that is by constriction due to increased fibrosis.

All postmortems and experiments in animals point to the fact that the greatest production of fibrosis occurs principally along the blood-vessels and bronchial walls. Gardner found that traversing the parenchyma of the lung are tortuous vascular and bronchial tubes, the walls of which have been converted into dense fibrotic tissue, concluding that the pneumothorax produces "an alteration consisting in the development of a fibrosis in the pleura and connective tissue coats of the blood vessels and bronchi." Bruns and Kauffman also came to the same conclusion after studying pneumothorax in animals.

Therefore, if we assume that the fibrotic changes in the bronchial walls are continuously increasing, it is easy to understand how this fibrosis, whose tendency is principally to contract, setting itself around the bronchi, acts as a gradually contracting medium, and by tightening encloses the bronchi, until it eventually produces their complete occlusion so that the cavity to which the bronchi lead is shut off from the outside air and its gaseous contents are gradually absorbed. In other words, it is a process similar to atrophic cirrhosis of the liver, where the fibrous tissue, in contracting, strangles the branches of the portal vein.

Our idea, however, is not a new one. The occurrence of bronchi contracted and completely closed is found in every postmortem of pulmonary tuberculosis with some amount of fibrosis, and in many instances it is impossible to pass a probe through them. As far back as 1909, Klebs, in his text book on *Tuberculosis* (4), says that: "The scar tissue in the lungs may compress the bronchi so that areas of alveoli collapse." Now if, instead of an area of alveoli, we consider a cavity, which may be compared to a large alveolus so far as air-contents and position are concerned, we can easily see how the phenomenon occurs. The lumen of the bronchus must become gradually obliterated until it completely disappears, closing in this way the communication of the cavity with the outside air. It is at this time that the sputum becomes negative and that the absorption of the air in the cavity starts to take place. The absorption goes on gradually and its rapidity is dependent on the more or less permeability of the fibrous coat surrounding it. If at this time we introduced a needle into the cavity, connected to a manometer, we would find very likely that the pressure inside of the cavity is negative, and if we took a specimen of its air we would find that the oxygen has

decreased and the CO_2 increased as compared with the outside air. It is at this time that the cavity starts to decrease in size and very rapidly disappears, without the use of any positive pressure at all.

This process explains in our opinion the phenomenon. The fact that these cavities have a "stem," may confirm our theory, because the "stem" may be nothing else than the bronchus filled with fibrotic tissue.

We have now decided that we will gradually discontinue artificial pneumothorax in cases presenting such a condition, naturally keeping our patients under constant fluoroscopic and radiographic control. If our idea should prove to be correct, the cavity should remain closed even when all the lung has reëxpanded and the patient should be considered as cured. In this way the duration of pneumothorax treatment would be in some cases considerably shortened.

CONCLUSIONS

1. Some cavities may disappear during pneumothorax by atelectasis. This atelectasis is produced by bronchial occlusion, which in its turn prevents atmospheric air from entering the cavity.

2. Bronchial occlusion is the result of a gradual fibrotic constriction of the bronchial walls.

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OCCLUSION OF THE TRACHEA AND BRONCHI BY A TUBERCULOUS PROCESS COMPLICATING PULMONARY TUBERCULOSIS

Case Report with Autopsy Findings[1]

MACK McCONKEY

Tuberculous disease, arising from the inner surface of the trachea and larger bronchi, ultimately leading to their occlusion, is a rare complication of pulmonary tuberculosis. The outspoken symptoms in the case here reported, combined with the physical and the radiographic examinations, pointed unmistakably to an obstruction in the lower respiratory tract.

Mrs. M.: Aged 27, was admitted to the sanatorium December 3, 1929. She said she had been in good health until about a year previously when she became irritable and lost her appetite. Four months later she had an acute attack of so-called asthma and laryngitis. Breathing was difficult, especially on expiration. Wheezes were heard in the chest, and a dry, hacking cough developed. She lost her voice and had pain on swallowing. The symptoms disappeared after a week of rest in bed, but four months later they reappeared in an aggravated form and the cough became productive for the first time. After a few weeks, the symptoms gradually abated, and when the patient came to us she complained of weakness, loss of appetite, and a slight cough with 8 cc. of sputum daily, mucopurulent and containing tubercle bacilli. The patient was pale, afebrile, poorly nourished; weight 97 lbs., height 5 feet, 1 inch.

Physical Examination

A tumor about the size of a small egg was found in the axilla on the left side. The patient said she discovered it about five years ago, but that it had not bothered her. It was firm and painless and the overlying skin was not implicated. The thorax was symmetrical but narrow and flat, and its excursion normal. There was moderate dulness over the upper third of the right lung. The breath-sounds in this region were feeble, and râles latent and numerous; otherwise, the physical examination was negative.

The chest roentgenogram (figure 1) presented a dense, uniform shadow at

[1] From the New York State Hospital for Incipient Tuberculosis, Ray Brook, New York.

the summit of the right lung-field, bound below by a sharp margin, which extended downward and inward and fused with the shadow of the mediastinum. There were mottled shadows in the right 1st and 2nd interspaces, and the trachea was deviated to the right.

Laboratory Findings

Haemoglobin and red blood cell count, normal; leucocytes 12,350; 36.5 per cent polymorphonuclears, 32.5 per cent small lymphocytes, 8.5 per cent large lymphocytes, 17.5 per cent monocytes, and 5 per cent eosinophiles. The urine was normal and the Wassermann test negative.

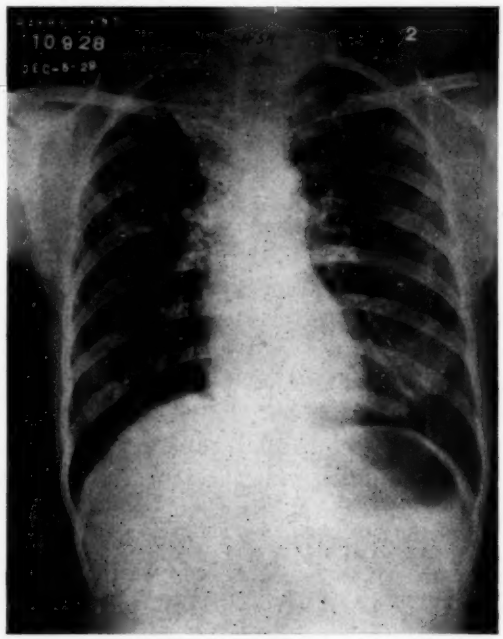


FIG. 1. Roentgenogram of chest taken on admission. There is evidence of disease from the summit of the right lung to the level of the third rib anteriorly. The homogeneous shadow at the summit of this lung bounded by a sharp lower border was thought to represent a contracted upper lobe.

One month after admission, the patient suffered from another attack of so-called asthma, attended by cyanosis, severe expiratory dyspnoea, loss of voice and pain on swallowing, temperature 100.6°, pulse rate 104, respiration 20 per minute. Aside from the physical signs previously noted, numerous sibilant rhonchi were heard over both lungs. The mucosa of the larynx was slightly injected and oedematous. The vocal cords were normal in appear-

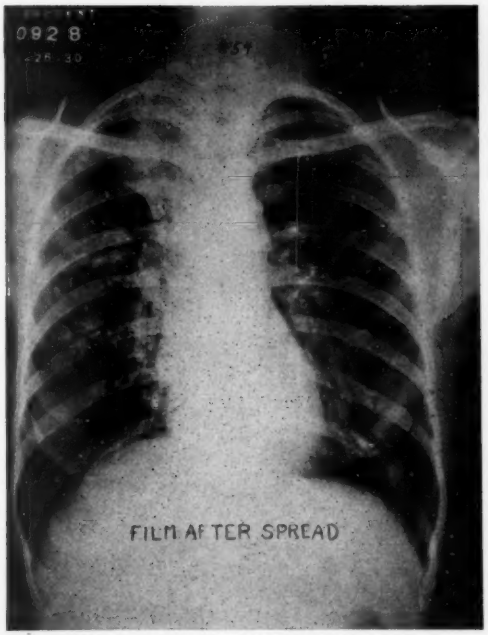
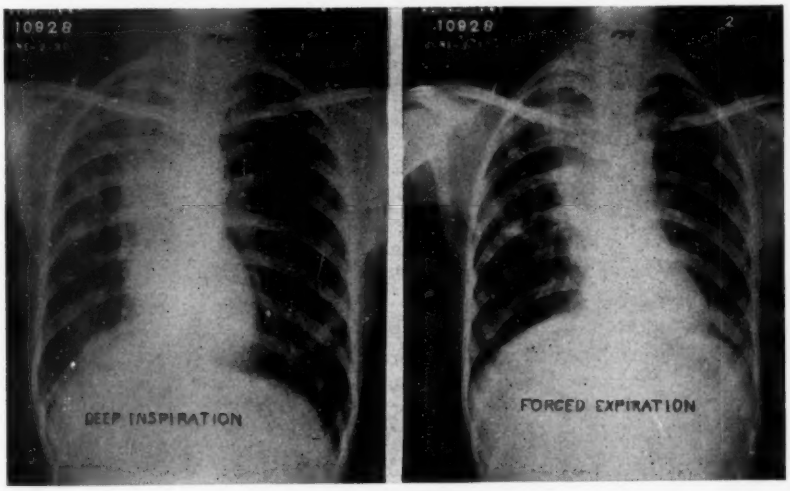


FIG. 2. Roentgenogram taken during the attack, which occurred a month after admission. Considerable new mottling is present in the 2nd and 3rd interspaces on the right. The shadow at the summit of this lung is less homogeneous and the straight lower border is less distinct and has descended.



A B

FIG. 3. Roentgenograms during an attack of dyspnoea about six months after admission. 3A was made at the height of inspiration and 3B on forced expiration a few seconds later. The right or affected lung neither inflates nor deflates normally. The mediastinum is displaced to the right on inspiration and to the left on expiration. The diaphragm on the right is immobile.

ance. A chest roentgenogram (figure 2), taken during this attack, showed that the shadow at the summit of the right lung-field had extended downward and its demarcation was less distinct, suggesting that the lung in this region had partially reëxpanded. The mottled shadows now extended down to the fourth rib. The attack subsided after a period of ten days but others recurred

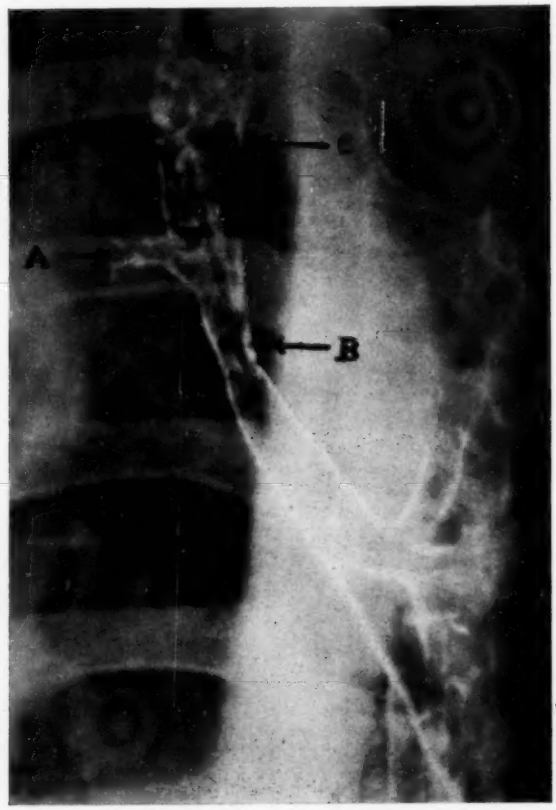


FIG. 4. Trachea and bronchi outlined with lipiodol while the patient reclined on the right side. The iodized oil flowed a short distance into the right main bronchus (A). The left main bronchus is narrowed at (B). At autopsy, an enlarged and partly caseous lymph node encroached upon the bronchus at this point. The trachea (C) does not appear constricted.

at intervals of two to three weeks. The one in June, six months after the patient came to us was of unusual severity and left her prostrated. Cyanosis was extreme, dyspnoea marked, expectoration copious and frothy, temperature 102°, pulse 136, and respirations 30 per minute. The right side of the chest was now practically immobile. The percussion note over the upper third of

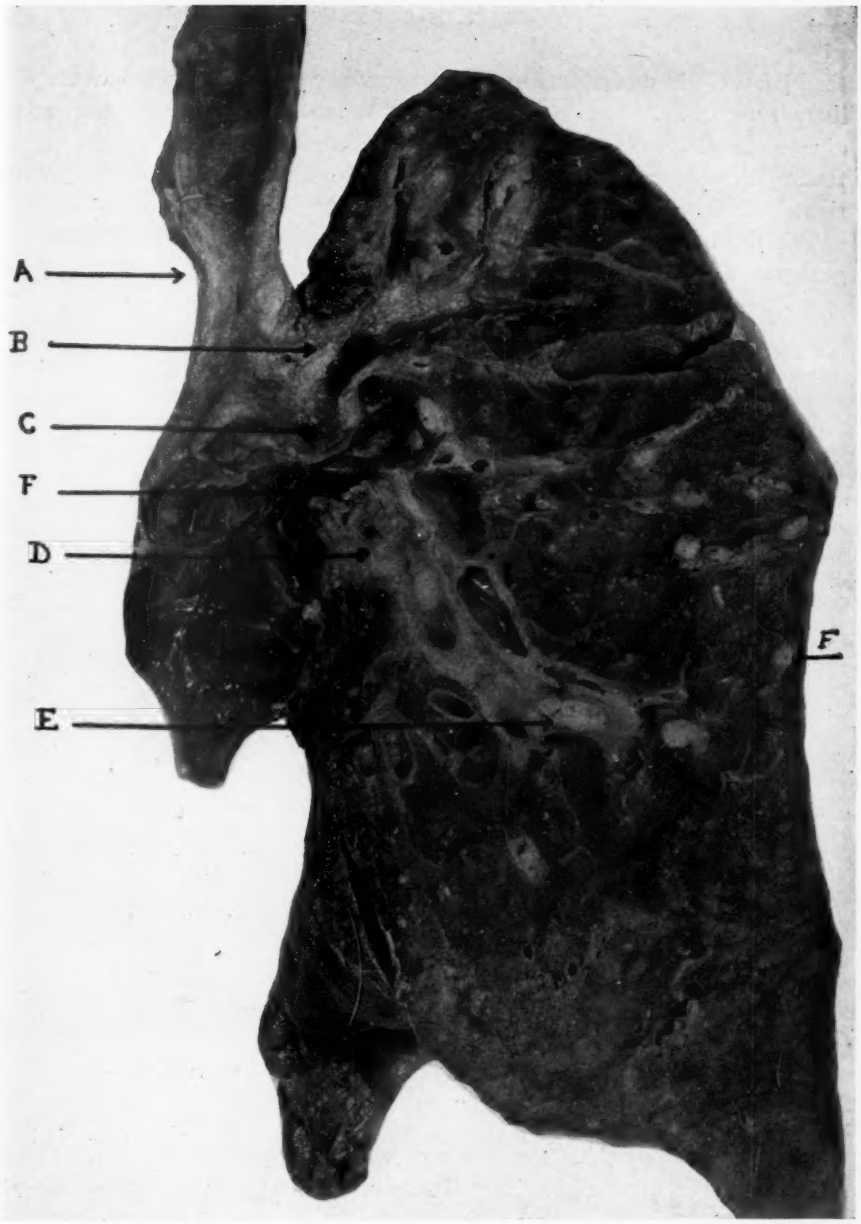


FIG. 5. Photograph of a sagittal section made through the trachea and main bronchi of the right lung viewed from the back. At (A) there is marked constriction of the trachea. The right main bronchus (C), the eparterial branch (B) and the lower lobe bronchus (D and E) are almost completely occluded with caseonecrotic débris. At (F) cross-section of a small bronchus almost occluded.

the lung was still moderately dull, but from this point to the base it was strikingly tympanitic. The breath-sounds were barely audible over the entire affected lung. Sonorous rhonchi, best heard at the end of expiration and at the beginning of inspiration, were present over both lungs, but louder over the right.

The right lung-field was much smaller than the left in the chest roentgenogram (figure 3A), taken at the height of inspiration, while the lung fields

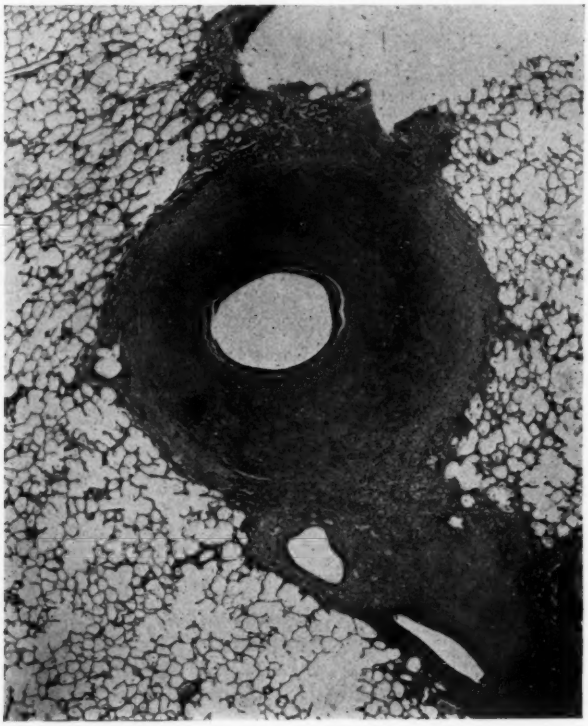


FIG. 6. Microphotograph (×30) of a small bronchus showing considerable caseation of its wall and marked narrowing of the lumen.

were approximately the same in size on the roentgenogram (figure 3B) taken at the end of forced expiration. These findings suggested that the air was trapped in the right lung. The diagonal chest roentgenogram (figure 4) following the intratracheal injection of lipiodol, showed the left main bronchus (B) outlined in its entirety, but only a small part of the proximal end of the right bronchus (A), despite the fact that the posture of the patient favored the flow of the lipiodol into the right bronchus.

The symptoms abated after two weeks and the patient appeared to be comfortable, but on August first, approximately eight months after the patient entered the sanatorium, alarming symptoms of obstruction of the lower air-passages developed; cyanosis was marked, and the respirations gradually became deeper, slower and more labored, and the patient died of suffocation a few hours later.

Autopsy Report

The body was emaciated. The tumor in the axilla on the left side proved to be tuberculous nodes firmly matted together. The capsule was dense and

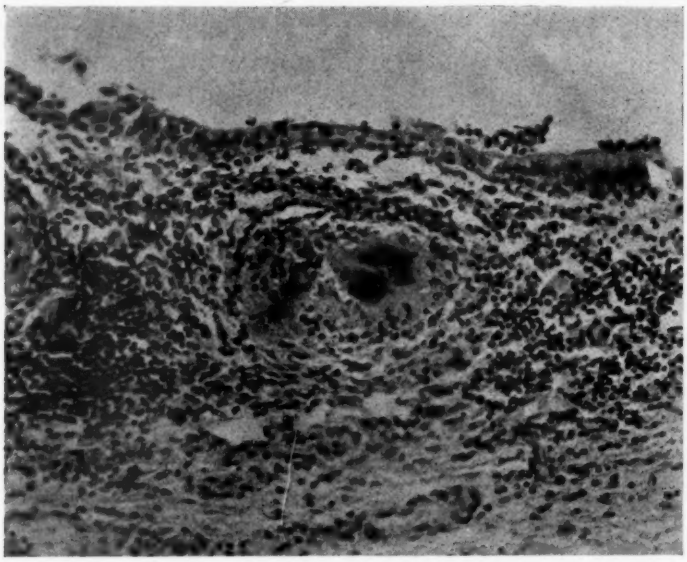


FIG. 7. A small noncaseous lesion beneath the intact bronchial mucosa. There is considerable round-cell infiltration and a giant cell without any evidence of caseation.

fibrous and enclosed inspissated caseous material. The right lung was firmly bound down by organized adhesions. When the lungs were excised, the right lung did not collapse, but the left did so in a normal manner. The right lung could not be inflated or deflated.

Sagittal sections of the lungs showed the upper lobe of the right lung to be markedly contracted with extensive areas of fibrocaseous disease. There were also numerous caseofibrous lesions in the middle and lower lobes and a few scattered lesions of the same nature in the lower lobe of the left lung. There was a marked stenosis of the lower part of the trachea (figure 5 (A)) due to a fibrocaseous, ulcerative lesion implicating the cartilaginous rings. The

right main bronchus and some of its major branches (figure 5 (B, C, D, and E)) were almost occluded with caseous material, while other bronchi (figure 5 (F)) presented varying degrees of involvement.

Figure 6 represents a cross-section of a small bronchus with a considerable amount of caseation, which narrowed but did not completely occlude the lumen. Tubercle bacilli were demonstrated in specially stained sections. Other bronchi (figure 7) presented only microscopic evidence of disease. Beneath the intact mucosa there were numerous round cells and a giant cell without evidence of caseation.

CONCLUSIONS

Tuberculous disease of the trachea leading ultimately to suffocation is a rare complication of pulmonary tuberculosis. Extensive implication of the bronchi is also an unusual feature. The clinical picture simulating that of asthma may be ascribed to the diseased bronchi. The physical and roentgenographic examinations pointed unmistakably to obstruction of the right main bronchus. The intratracheal lipiodol study (figure 4 (C)) six weeks before death failed to reveal evidence of the tracheal stenosis which caused death. Bronchoscopic treatments might have relieved the patient, at least temporarily.

PULMONARY ASPERGILLOSIS IN ASSOCIATION WITH BRONCHIAL CARCINOMA[1]

R. H. KAMPMEIER AND H. A. BLACK

Since 1847, when pulmonary aspergillosis was first described, there has been much discussion on the question of whether this infection is primary or secondary. Primary infection of the lung has been only rarely reported by American authors. Generally writers in this country are very loath to accept primary infection, and many even question the pathogenicity of the organism under any circumstances. Among European authors, especially the French, primary pulmonary aspergillosis is accepted as an entity and is not infrequently reported as such. Some even believe this infection to be primary in the presence of tuberculosis, considering the latter to be secondary. Their reasoning is that since the fungus is so universally present it should be found much more frequently in association with tuberculosis than it is, if it is secondary.

In the literature, the discussion of aspergillus as a secondary invader is limited almost entirely to its association with tuberculosis. Occasionally mention is made of its presence in lung abscess or in bronchiectasis. However in this literature as well as in the recent extensive literature on carcinoma of the bronchi and lungs, no specific reference has been found of aspergillus infection secondary to carcinoma. Castellani (1), Hamman (2), and Lapenta (3), who have discussed the secondary infections with aspergillus, make no reference to this possibility.

Therefore it seems warranted to report a case in which aspergillosis occurred in the presence of a bronchial carcinoma. Thus the profession may be acquainted with this possibility, since the tendency of some authors has been to accept aspergillus infection as being primary if repeated examination does not show the tubercle bacillus to be present in the sputum.

Case Report

The patient, a white male aged 57 years, was first seen February 2, 1931. The complaint was pain in the left chest and cough. *Present Illness:* Though

[1] From the Department of Medicine, Louisiana State University Medical Center, New Orleans, Louisiana, and the Pueblo Clinic, Pueblo, Colorado, respectively.

there had been a little cough with purulent sputum since May, 1930, the patient first became aware of ill health about 3 months before he was first seen, when he began to suffer from drenching night-sweats. Cough had increased recently, occurring usually in the morning, with a small amount of sputum, but no haemoptysis. The appearance of pain in the left chest, anteriorly, three days before finally forced the patient to see a physician. Pain was constant and not related to respiration. Ease of fatigue had been noted for 4 months. There had been loss of 10 pounds of weight in 6 months. *Past History:* Negative. *Family History:* Of interest was the fact that one sister had died of gastric carcinoma. *Social History:* The patient had been a heavy pipe-smoker for years. For twenty years he had been the proprietor of a dyeing and cleaning shop. Before that he had been a wool-dyer.

Physical Examination: Only points of interest will be recorded. The patient was a short, slender male weighing 117 pounds. Dyspnoea was obvious when he was speaking. Chest emphysematous; lagging on deep inspiration present on the left. Tactile fremitus absent over the front, bilaterally. Percussion note impaired over the left apex, anteriorly and posteriorly. In front the note was flat over the 2nd to 4th interspaces and laterally to the anterior axillary line. Elsewhere over the lung-fields the percussion note was characteristic of emphysema. Breath-sounds were practically absent over the upper left chest. No râles were heard. Clubbing of finger tips and incurvature of the nails were present. Temperature normal.

Tentative Diagnosis: Bronchogenic carcinoma.

Laboratory Data: Haemoglobin (Dare) 63 per cent; red cell count 4,800,000, and white cell count 20,000; 80 per cent polymorphonuclear cells, with shift to left (Arneth-Schilling). Blood Wassermann and Kahn tests negative. Sputum negative for tubercle bacilli. Stereoscopic chest plates showed shadow in left hilum compatible with neoplasm. A lacy infiltration was present in the left lower lobe. (Figure 1.)

Clinical Course: Because of roentgenological findings in left lower lobe, the sputum was repeatedly examined for fungi. After potassium iodide for about a week, the sixth sputum examination disclosed mycelial threads and clumps of spores. After this the fungus was found at all sputum examinations, seventeen in number, but tubercle bacilli were never found. A pure culture of aspergillus was grown from the sputum on Sabourraud's medium; conidia and nonsegmented mycelia were present. An emulsion of this was injected intraperitoneally into a guinea pig, and at autopsy 6 weeks later no lesions were found. Culture of sputum on glycerine-potato medium was negative for tubercle bacilli.

Leucocytosis of 15,000 to 20,000, with shift to the left in polymorphonuclear cells persisted to death. No anaemia developed. The patient gradually lost weight, and by June had become noticeably weaker. Paroxysmal cough was

severe. Dyspnoea upon exertion and speaking became progressively worse. In the latter part of April the sputum became more profuse, and from then until death showed almost constant streaking with blood. The physical signs did not change a great deal at any time. Breath-sounds became more bronchial in character in the last 2 months of life.

Deep roentgen-ray therapy was used on four occasions over the left hilum. Potassium iodide in large doses and sodium cacodylate were used because of the possible pathogenicity of the fungus. Marked clearing of the lower-lobe shadow occurred in the first few weeks and did not recur in successive plates. (Figure 2.)

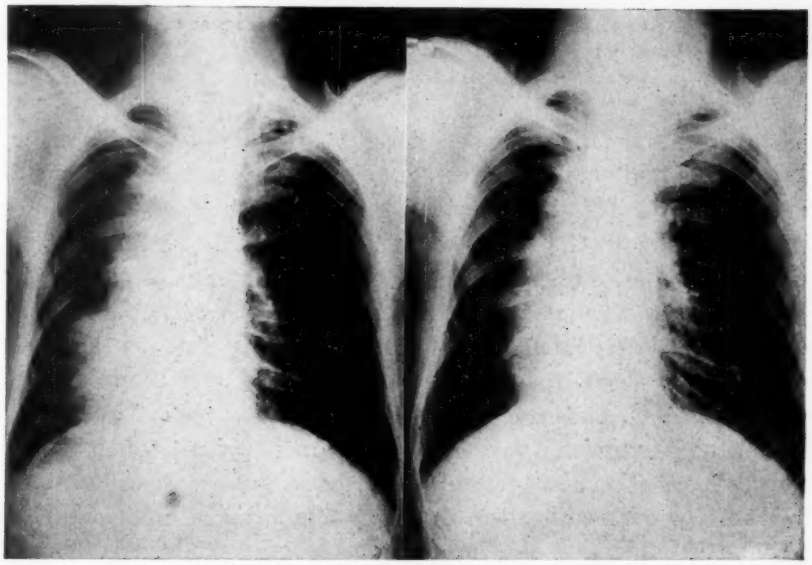


FIG. 1 FIG. 2

For description see text

On July 8, five months after he was first seen, the patient died of massive pulmonary haemorrhage during a paroxysm of coughing.

Autopsy: This was done by one of us (R. H. K.). Upon opening the thorax dense adhesions were found over the anterior aspect of the left lung and in the axilla. At the hilum of the left lung was palpated a hard, irregular mass. Lungs and mediastinal structures were removed en bloc, and the trachea and bronchi opened posteriorly. About 4 cm. from the tracheal bifurcation, in the left main bronchus was an irregular, nodular mass involving its whole circumference. The opening through this mass led into a cavity 3.5 cm. in diameter

with necrotic walls. Two blood-vessels led across the cavity without any supporting structure. A fresh clot filled the cavity, bleeding having taken place from one of these vessels. On incision, there was found in the lower lobe a central area, about 7 cm. in diameter, in which the lung tissue was infiltrated and more solid. From this area and the bronchioles in the area could be expressed thick pus. This was not present at the periphery of the lobe nor in the upper lobe. The right lung was negative. Microscopic examination by Dr. C. W. Maynard was reported as follows.

The wall of the cavity is densely infiltrated with irregular masses of poorly differentiated epithelial-type cells with many mitoses. An occasional area is better differentiated, the cells showing spines, and being more regular in shape. Many large single nucleoli are present. Smears of pus are packed with large oval spores. Diagnosis is squamous-cell carcinoma of bronchus with secondary aspergillosis.

COMMENT

The correct diagnosis was made, tentatively at first, on the history and physical examination. However, some doubt was cast by the constant presence of the aspergillus in the sputum without tubercle bacilli. The roentgen shadow in the left lower lobe could not be satisfactorily explained on the basis of bronchogenic malignant tumor as could the hilum shadow which was compatible with such a diagnosis. The fact that the lower-lobe shadow cleared a great deal by use of potassium iodide also was confusing. Deep roentgen therapy was used over the hilum however. (Dr. C. O. Giese, of Colorado Springs, saw the patient in consultation and committed himself to a diagnosis of malignant tumor.) Because of retention of secretion due to the neoplasm, the fungus probably had a good medium for growth. Whether the organism was a factor in the production of symptoms, and whether it aided in tissue destruction in the carcinomatous area is a matter for speculation.

DISCUSSION

It is conceivable that confusion in diagnosis might arise at times between aspergillosis and malignant tumor. In the case reported here, on the basis of carcinoma, we have practically all the symptoms outlined by Schneider (4) for fungus infection of the lung. These are insidious onset, anorexia, night-sweats, loss of strength, productive cough, purulent sputum often blood-tinged, and haemoptysis. When the roentgenological aspects are considered, we note that Hamman (2) states that pneumonomycosis among other things may suggest new growth, and that a lesion of the hilum and lower lobes suggests fungi.

Bronchogenic carcinoma should be considered in a case such as reported, even though a diagnosis of aspergillosis seems compatible with symptoms, signs and roentgenological findings. Bronchoscopy is indicated to assist in the diagnosis. In our case it was recommended, but under the circumstances was not urged against the patient's wishes.

SUMMARY

A case of pulmonary aspergillosis secondary to a carcinoma of the bronchus has been reported. Though the aspergillus is usually found secondary to tuberculosis, it is clear that the absence of tubercle bacilli from sputum containing the fungus does not necessarily permit a diagnosis of primary pulmonary aspergillosis.

Acknowledgment is due Dr. C. W. Maynard of the Pueblo Clinic for the laboratory studies.

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A CLINICAL STUDY OF ALLERGY AND IMMUNITY[1]

A. A. KARAN AND V. H. DANFORD

The literature on tuberculosis abounds with attempts to correlate allergy and immunity. The observations of Patterson (1), Krause and Peters (2), Soper (3), Long (4), Rist and Rolland (5), Willis (6), Manwaring and Bronfenbrenner (7), Krause (8) and others have definitely demonstrated that sensitized animals are more resistant to tuberculous infection than nonsensitized animals. As a result of these studies, allergy and immunity in tuberculosis have been regarded as parallel and interdependent phenomena. Citation of a few, of the numerous, statements found in the literature will serve to illustrate the accepted correlation between allergy and immunity. Myers (9) claims that: "The degree of allergy apparently ebbs and flows with the activity or latency of a tuberculous lesion and with the presence and absence of reinfection." Baldwin, Petroff and Gardner (10) state that: "The tuberculin reaction afterward (after infection) mirrors the succession of events from the time of tubercle formation through the successive stages of healing or progression." Or (10), "Generally, susceptibility to reaction (tuberculin) parallels the extent of the disease, but a high sensitiveness may be present with a slight amount of disease if this has been recently progressive." Again (10), "The hypersensitive individual is subject to changes in reactivity during the course of tuberculous infection or disease. The degree of sensitiveness is, to a large extent, a reflection of the process taking place in the focus."

Krause (11), correlating the intensity of the cutaneous tuberculin reaction with the progress of tuberculous disease in guinea pigs, found that

> The series of gunea pigs inoculated with H37 displayed increasing cutaneous hypersensitiveness (measured by diameters of redness and induration and diameters of haemorrhagic necrosis) from eleven days after infection, when the first regional glandular changes were noted, up to forty-six days, when the disease was well advanced. At every stage, too, their reactions were more intense than those in guinea pigs suffering from R1 self-limited tuberculosis.

[1] From the State Sanatorium, Wallum Lake, Rhode Island.

From his study Krause (11) concludes that cutaneous hypersensitiveness increases with progressive disease; varies directly with the extent and intensity of the disease; diminishes with healing of disease and is increased by reinfection.

On the other hand, Rich and McCordock (12), while admitting "that the bacilli (tubercle) can not thrive as well in the previously infected body as in the normal one," claim that

> the bodily change responsible for this acquired interference with the life of the bacillus is, in whatever it consists, quite separate and distinct from the forces which are concerned in the allergic inflammatory necrotizing tendency. Indeed, in favor of the idea that "immunity is achieved through allergy" we have, really, only the fact that, in the experimental animal, both immunity and allergy appear at about the same time after infection, and that they are usually co-existent thereafter. It is, however, by no means established that they are invariably co-existent.

On the clinical side, the observations of Holmes (13) tend to corroborate the findings of workers with experimental animals who regard the intensity of the cutaneous tuberculin reaction as reflecting the pathological changes in the body. In tuberculous patients, at regular intervals, Holmes measured the intensity of the cutaneous tuberculin reaction while observing changes in their clinical condition. No mention is made in the article of any roentgenological studies. While admitting exceptions, the writer concludes that:

> Individuals suffering from pulmonary tuberculosis present marked tuberculin hypersensitiveness soon after the clinical onset of the disease. This hypersensitiveness diminishes if they improve and fluctuates or remains stationary, if they do not improve. More advanced cases, in time of exacerbation, present this elevated hypersensitiveness again; it rises or falls, following more or less closely the clinical course of the disease. Toward death, it may rise much higher, and then fall until it fails entirely.

It might be added that Holmes could find no correlation between the degrees of hypersensitiveness and the amount of pulmonary involvement present. He also failed to find any definite interval between the appearance of an exacerbation and the development of hypersensitiveness.

Lange (14), in a study of skin sensitiveness to the intracutaneous injection of tuberculin in healthy children, suspects, lymph-node and bone tuberculosis and pulmonary tuberculosis, found no correlation

between the intensity of the reaction and the tuberculous process. In bone and lymphatic tuberculosis the intensity of the skin reaction was particularly marked. The healthy children, and to a lesser degree the suspects, showed greater allergy than those with pulmonary tuberculosis. The author failed to find any correlation between the intensity of the tuberculin reaction and the type, extent, course of the disease, age of the disease-process, fever-reaction and nutrition of the patient.

It is apparent that investigators, particularly clinicians, who have attempted to correlate allergy and immunity, have arrived at contradictory conclusions. An additional clinical study of the problem was, therefore, thought to be of interest.

In selecting patients for observation it seemed desirable to choose those in whom rapid clinical changes might be expected. Thus, all the 40 patients included in this investigation had one, or a combination of, collapse-therapy measures instituted while they were under observation. The patients ranged in age from 15 to 63 years. The lesions in these patients varied from the unilateral pneumonic to the bilateral fibrocavernous.

METHOD OF STUDY

The tuberculin used in this study was a preparation of O. T. marketed by Sharp and Dohme. Aronson (15), Mariette and Fenger (16), Lewis and Aronson (17) and Wells and Long (18) found that samples of commercial tuberculin vary in potency, and therefore recommended that tuberculin be standardized on the basis of its skin-testing potency rather than on its guinea-pig-killing potency. Information (19) obtained from Sharp and Dohme showed that the tuberculin employed in this investigation was standardized by means of the intracutaneous test on both normal and tuberculous guinea pigs against a standard control tuberculin furnished by the British Medical Research Council. At any rate, in order to make certain that tuberculin of equal potency was being used throughout this study, frequently prepared fresh dilutions of one concentrated sample were employed for intracutaneous injection. For this reason comparison of variations in intensity of the tuberculin reaction in successive tests in one patient, or in the entire group, could only be accounted for by differences in sensitiveness, and not by difference in tuberculin potency.

The dosage used in each instance was the same: it consisted of the intracutaneous injection of 0.1 cc. of a 1:1000 dilution of tuberculin on

the flexor surface of the forearm. Injection of tuberculin more than once in the same place was avoided. After 24 and 48 hours, the long and short diameters of the resulting areas of redness and induration were measured. Since the usual reacting surface of the skin is elliptical rather than circular, it was considered more accurate to estimate the surface areas of redness and induration as if they were ellipses. The following formula was found to be the most accurate one for estimating surface areas of ellipses: $A = 0.7854SL$, where A = surface area, S = short diameter, and L = long diameter.

The group selected for study was comprised entirely of male patients. This obviated the possible confusing observations which might be noted in female patients during menstruation or pregnancy.

The routine followed in each case consisted of an intracutaneous tuberculin test several days before collapse therapy was instituted. The test was repeated monthly for six successive months. The clinical course of each patient was observed very carefully, and roentgenological studies were frequently made. At the completion of the period of observation curves of the intensity of the tuberculin reactions were charted on graphs; an attempt was made to correlate these with the clinical pictures and roentgenological evidence.

RESULTS

From the collected data an attempt was made to answer the following questions: *1:* Does the intensity of the tuberculin reaction increase or diminish when the patient's condition is improved? *2:* Does the tuberculin reaction increase or diminish with progressive disease? *3:* Is there any correlation between the intensity of the tuberculin reaction and the type of tuberculous disease? *4:* Does the peak of the intensity of the tuberculin reaction (at 24 or 48 hours) bear any relationship to the type of lesion, and does it reveal any correlation to progression or retrogression of the disease? *5:* Is there any typical curve in patients who show improvement and those who do not improve?

After careful study of the graphs, clinical records and roentgenograms of the entire group, no positive conclusions could be drawn. Tabulation of the possible correlation between the intensity of the tuberculin reaction and character of lesion, fever-reaction, disappearance of tubercle bacilli from sputum, roentgenographic evidence of healing or progression of the disease and loss or gain in weight were utterly contradictory. In the groups as a whole, the tables showed contradictory results in both the

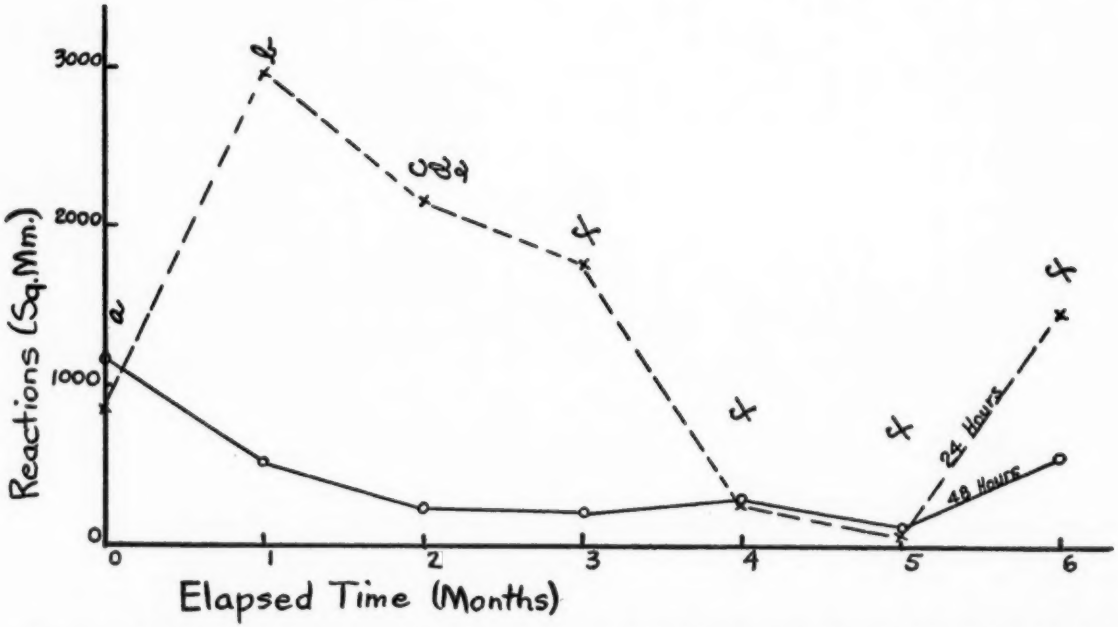

CHART 1. Male, age 37. Fibrocaseous tuberculosis, left lung with cavity-formation. Scattered fibrosis in right lung. Broken line, 24-hour reading of tuberculin reaction; solid line, 48-hour reading of tuberculin reaction; a, reaction before induction of artificial pneumothorax; b, tuberculin reaction one month after induction of artificial pneumothorax; c, sputum became negative; d, closure of cavity; e, roentgenographic evidence of healing; f, satisfactory progress.

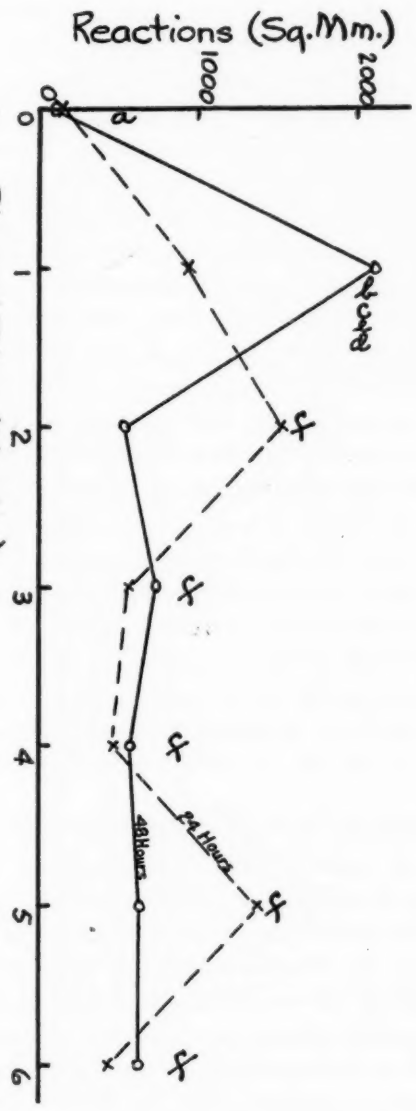

CHART 2. Male, age 56. Fibrocaseous tuberculosis right lung with cavity-formation. Scattered fibrosis in left lung. Lines and letters indicate the same observations as in chart 1.

24- and 48-hour readings of the intensity of the reactions when compared with the progress of the disease. Equally incongruous results were noted when the successive monthly reactions in individual patients were compared with the progress of the disease. It is evident that the questions set down previously were all answered in the negative. Charts 1 and 2 show this graphically. It might be mentioned that it seemed preferable, for purposes of illustration, to present these two graphs rather than to include the confusing tables.

Krause (11) explains the failure of correlation between the cutaneous reaction and the clinical progress in tuberculous patients on the basis of the existing anatomical and physiological complexity of the disease. The vast majority of the patients in this study presented fibrocaseous lesions. It is obvious that all the destructive and reparative processes would be encountered in such a group of patients, and, in many individual patients, all stages of healing and breaking-down could be present at the same time. It seemed interesting, therefore, to attempt to correlate the cutaneous tuberculin reaction with the progress of patients in whom the clinical disease revealed the least complex anatomical form.

A review of data showed that 5 patients out of the entire group had acute, recent unilateral exudative or pneumonic tuberculosis. They were all from 15 to 21 years of age. In three, the onset of clinical tuberculosis was definitely known, because they had been observed frequently and had roentgenograms prior to the onset of clinical tuberculosis. In the other two patients, although no roentgenograms were available before the onset of the disease, all the evidence pointed to a recent acute onset.

These five patients were divided into two groups. Three in the first group improved considerably. The graphs of these patients, which represented the intensity of the cutaneous reactions, showed no definite correlation, from month to month, in the individual patient, between the intensity of the reactions and the progress of the disease. The attempt to correlate the record of one patient with the others also failed.

In the two patients of the second group, although there was evidence of improvement in their general condition, the progression of their tuberculosis remained unchanged after the second or third month. Both patients had considerable collapse of their diseased lungs, but in each case a cavity remained open. The graphic representation of the curves of the intensity of the tuberculin reactions showed marked variation in both the 24- and 48-hour surface areas of cutaneous reaction.

COMMENT

It is evident from the data collected that attempted correlation between the intensity of the intracutaneous tuberculin reaction, which is an indication of allergy, and the clinical progress of a patient, gave negative results. In other words, a parallelism and interdependence between allergy and immunity, in the group of patients observed, could not be established. The reason for the failure in correlating these two phenomena is very aptly explained by Pinner (20). The term allergy is used to indicate a known effect of a known cause; that is, the altered reactivity of the organism following an infection. Immunity "is not defined by its causation, but by the ultimate aim it is expected to accomplish." It is apparent that allergy and immunity are incomparable concepts. For this reason, attempts to measure one of these two phenomena in terms of the other results in failure.

CONCLUSIONS

1. An attempt to correlate the intensity of the intracutaneous tuberculin reaction with the clinical progress, in a group of 40 tuberculous patients receiving collapse therapy, gave negative results.

2. The intracutaneous tuberculin test, before collapse therapy was instituted in this group of patients, failed to reveal any correlation between the intensity of the reaction and the type of disease.

3. Graphs of the successive reactions in each patient did not disclose any typical curve in patients who improved and in those with progressive disease.

The authors wish to express their gratitude to Mr. Robert Mackie for his aid in preparing the graphs.

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FURTHER EXPERIENCES WITH MA-100 PROTEINS[1]

E. P. K. FENGER,[2] E. S. MARIETTE,[2] DOROTHY W. HUTCHINSON[3] AND A. J. OUELLETE[3]

As a result of previous comparative studies with Dorset's Old Tuberculin and the MA-100 proteins of the human, bovine and avian tubercle bacillus and the timothy-grass bacillus, two (1) of us concluded that the MA-100 Human Protein was a more sensitive and selective testing agent than Old Tuberculin. Therefore it has been used as the standard for routine skin tests in the Sanatorium and the Out-Patient Department since then. We also concluded that the MA-100 proteins were apparently nonspecific in large doses at least. Another conclusion was that there is a protein substance common to all acid-fast bacilli which if given in a large enough dose will elicit the same type of reaction as that obtained from Old Tuberculin. While no conclusion was drawn about the degree of stability of the MA-100 proteins, we felt that the proteins were fairly stable.

This report is based on skin tests on approximately 7,000 individuals and covers further studies on these conclusions and presents some other problems which may be of interest in epidemiological studies. These studies were carried on as part of the coöperative program of the Medical Research Committee of the National Tuberculosis Association. The materials used in the skin tests were furnished by the H. K. Mulford Laboratories of the Sharp and Dohme Company.

Is the MA-100 Human Protein stable when diluted? The Ma-100 protein in its preparation has not been subjected to any denaturing process with heat or a chemical. It is precipitated from the filtrate at a definite isoelectric point and the diluent is normal saline solution. Thus the testing substance when purchased from the manufacturer already diluted contains no preservative of phenol or glycerine (2). The importance of the question of its stability is thus evident. In an attempt to determine

[1] Presented at the twenty-ninth annual meeting of the National Tuberculosis Association, Toronto, Ontario, June 30, 1933.

[2] From the Glen Lake Sanatorium, Oak Terrace, Minnesota, and the Department of Medicine, University of Minnesota, Minneapolis, Minnesota.

[3] Minneapolis, Minnesota.

the stability of the MA-100 Human Protein, 231 individuals were tested with 0.000,5 mgm. of the MA-100 Human Protein, and 0.01 mgm. of Dorset's Old Tuberculin in fresh dilutions and in dilutions about fourteen months old. Of the group tested, 88.7 per cent reacted positively to the fresh and 87.9 per cent reacted positively to the old dilution of the MA-100 Human Protein, while 83.1 per cent reacted positively to the fresh and 82.7 per cent reacted positively to the old dilution of Dorset's Old Tuberculin. Thus a larger percentage of individuals reacted positively to the dilution of the MA-100 Human Protein fourteen months old than to the fresh dilution of Dorset's Old Tuberculin. It therefore appears that the MA-100 Human Protein in dilutions of at least a year old is stable and gives a higher percentage of positive reactions than does the fresh dilution of Old Tuberculin.

Should a preservative be added to the dilutions of the MA-100 Human Protein? In consideration of this question, 106 individuals were tested with 0.000,5 mgm. of the MA-100 Human Protein without a preservative and with 0.000,5 mgm. and 0.000,1 mgm. respectively of the same protein containing a mercurial preservative in the strength of 1–5,000 known to the Mulford Laboratories as No. 186. Of the group tested, 81.8 per cent reacted positively to 0.000,5 mgm. of the MA-100 Human Protein without a preservative while 90.9 per cent reacted positively to dilutions of the same protein containing a preservative. Thus a larger percentage of individuals reacted positively to dilutions of the MA-100 Human Protein containing a mercurial preservative irrespective of the dose used than to 0.000,5 mgm. of the MA-100 Human Protein without a preservative.

The reaction to the dilution with the preservative, however, is atypical. In most instances there is little or no erythema. When it is present, however, it may be pale or of the usual color but the induration is shot-like and deep and suggestive of a small lump under the skin or very deep in the skin. This centrally located, deep, shot-like induration is present whether or not the reaction appears typical.

In a further study of this subject, 16 individuals were tested with 0.000,001 mgm. of the MA-100 Lepra Protein containing the same preservative and 93.8 per cent reacted positively. In this series also the positive reactions were of the same general atypical character as those observed in the group tested with dilutions of the MA-100 Human Protein containing the same preservative.

From the above series of tests, we can conclude that the mercurial preservative acts somewhat as a foreign body and produces an atypical

induration which clouds the reaction and which therefore can be considered as a false positive. Because of this we believe its further use is not warranted.

Are the MA-100 Proteins specific or is there a protein substance common to all acid-fast bacilli which if given in the proper dose will elicit the same general type of a reaction as that produced by Old Tuberculin? These two questions will be considered together because they are so closely allied. In the previous studies (1) of the MA-100 proteins reported on in 1931

TABLE 1

General-population group

AGE GROUPS	O.T., 0.01 MGM.		O.T. DORSET, 0.000,01 CC.		H 37 M.A. 100, 0.000,5 MGM.		M.A. 100 BOVINE, 0.000,1 MGM.		M.A. 100 AVIAN, 0.001 MGM.		M.A. 100 TIMOTHY, 0.01 MGM.	
	Number tested	Per cent positive	Number tested	Per cent positive	Number tested	Per cent positive	Number tested	Per cent positive	Number tested	Per cent positive	Number tested	Per cent positive
0– 4	16	0	8	12.5	8	12.5	0	0	0	0	0	0
5– 9	494	10.7	602	8.3	383	3.9	84	7.1	56	8.9	79	24.1
10–14	526	17.3	587	8.7	241	14.1	127	6.3	117	21.4	102	43.1
15–19	139	24.5	284	16.9	116	25.0	56	14.3	43	25.6	69	53.6
20–39	27	44.4	413	37.3	144	44.4	98	40.8	82	54.9	89	65.2
Total.....	1,202	15.8	1,894	16.1	892	16.0	365	17.0	298	28.9	339	46.6
REPEAT DOSE 1.0 MGM.												
0– 4	16	18.7										
5– 9	441	29.5										
10–14	435	51.3										
15–19	105	57.1										
20–39	15	53.3										
Total.....	1,012	41.9										
Grand total.....	1,202	51.1	1,894	16.1	892	16.0	365	17.0	298	28.9	339	46.6

we were impressed with the high percentage of positive reactors to the MA-100 Timothy Protein as compared with the percentage of positive reactors to the MA-100 Human Protein and to Dorset's Old Tuberculin. This is well shown in table 1 which was included in the previous report and is repeated here merely to give a foundation for the present study.

This table compares results obtained by Aronson (1) (3) on 1,202 individuals tested with 0.01 mgm. as the initial dose and 1.0 mgm. as the repeat dose of Old Tuberculin and 1,894 individuals tested by Mariette and Fenger with 0.000,01 cc. (0.01 mgm.) of Dorset's Old Tuberculin

and the different MA-100 proteins in the doses listed. Aronson obtained 15.8 per cent positive reactors to the initial dose of Old Tuberculin. In our series 16.1 per cent reacted positively to Dorset's Old Tuberculin and 16 per cent reacted positively to the MA-100 Human Protein. As these two percentages are essentially the same as those obtained by Aronson, we can conclude that the incidence of infection in the two localities is essentially the same and also that the testing dose of the MA-100 Human Protein is correct. Therefore, whatever differences there may be in the percentage of the positive reactors to Dorset's Old Tuberculin and the other MA-100 proteins must be due to some other factor, probably a difference in the protein.

Those who failed to react to Aronson's original dose (0.01 mgm.) of O.T. were retested with 1.0 mgm., and 41.9 per cent of these reacted positively to this dosage. If we combine the positive reactors to Aronson's initial and repeat dose, we find that 51.1 per cent of the people tested reacted positively to Old Tuberculin. This is only slightly greater than the 46.6 per cent who reacted positively to the MA-100 Timothy Protein in our series. In comparing these two figures one should remember that the repeat dose of Old Tuberculin in Aronson's series is one hundred times as strong as his initial dose and five times as strong as the dose of the MA-100 Timothy Protein.

The present study of why so many individuals reacted positively to the MA-100 Timothy Protein as compared with the MA-100 Protein from the human tubercle bacillus or the bovine tubercle bacillus consists of the results of the tests on 6,295 individuals as shown in table 2.

Considering the group as a whole, we find that 21.7 per cent reacted positively to 0.000,5 mgm. of the MA-100 Human Protein while 56.6 per cent of those tested with 0.01 mgm. of the MA-100 Timothy Protein reacted positively, and 20 per cent of those tested with 0.000,5 mgm. of the MA-100 Timothy Protein reacted positively while only 1.9 per cent of those tested with 0.000,1 mgm. of the MA-100 Bovine Protein reacted positively.

This series is divided into three groups according to the dose and type of testing substance used. Group 1 consists of 4,498 individuals who were tested with 0.000,5 mgm. of the MA-100 Human Protein and 0.01 mgm. of the MA-100 Timothy Protein. Considering group 1 as a whole we find that 24.5 per cent reacted positively to the MA-100 Human Protein in contrast to 56.6 per cent who reacted positively to the MA-100 Timothy Protein. Group 1 is subdivided into two groups: (a) comprising

731 individuals tested at the Sanatorium and (b) a group of 3,767 school-children in rural Hennepin County. Subgroup (a) includes Sanatorium employees, Sanatorium patients, both adults and children, a general-population group of student nurses and medical students. Considering this subgroup as a whole, we find that 75.3 per cent reacted positively to the MA-100 Human Protein in contrast to 88 per cent who reacted positively to the MA-100 Timothy Protein. The percentage of the positive reactors to the two testing substances in the various units comprising

TABLE 2

Percentage of positive reactors to the M.A. 100 proteins

GROUP		NUMBER TESTED	HUMAN, 0.000,5 MGM.		TIMOTHY, 0.01 MGM.		TIMOTHY, 0.000,5 MGM.		BOVINE, 0.000,1 MGM.	
			Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
1a.	Sanatorium patients:									
	Adults	347	297	85.6	303	87.3				
	Children	55	46	83.6	47	85.5				
	Sanatorium employees	249	169	67.9	225	90.4				
	General population, adults	80	39	48.8	68	85.0				
	Subtotal	731	551	75.3	643	88.0				
1b.	Children	3,767	550	14.6	1,905	50.6				
	Subtotal	4,498	1,101	24.5	2,548	56.6				
2.	Children	1,483	220	15.0			297	20.0		
3.	Children	314	47	15.0					6	1.9
	Total	6,295	1,368	21.7	2,548*	56.6*	297*	20.0*	6	1.9

* Excluding those not tested with this substance.

subgroup (a) can be seen in the table. Suffice it to say that where active tuberculosis is present, there is only a slight difference in the percentage of positive reactors to the two testing substances, but in the units of well individuals, where tuberculosis may or may not exist, the percentage of positive reactors to the MA-100 Timothy Protein is much larger than the percentage of positive reactors to the MA-100 Human Protein.

Considering subgroup (b), that of 3,767 school children in rural Hennepin County, as a whole, we find that 14.6 per cent reacted positively to the MA-100 Human Protein while 50.6 per cent reacted positively to the MA-100 Timothy Protein.

Group 2 consists of 1,483 school children tested with the same dose (0.000,5 mgm.) of both the MA-100 Human Protein and the MA-100 Timothy Protein. In this group 15 per cent reacted positively to the MA-100 Human Protein while 20 per cent reacted positively to the MA-100 Timothy Protein.

Group 3 consists of 314 school children who were tested with 0.000,5 mgm. of the MA-100 Human Protein and 0.000,1 mgm. of the MA-100 Bovine Protein. In this series 15 per cent reacted positively to the MA-100 Human Protein, while 1.9 per cent reacted positively to the MA-100 Bovine Protein. We believe that the low incidence of positive reactors

TABLE 3

Correlation of X-ray and skin reactions on 731 individuals tested with 0.000,5 mgm. of the M.A. 100 Human Protein and 0.01 mgm. of the M.A. 100 Timothy Protein

NUMBER TESTED	GROUP	X-RAY POSITIVE FOR TUBERCULOSIS					X-RAY NEGATIVE FOR TUBERCULOSIS				
		Total number	Human		Timothy		Total number	Human		Timothy	
			Number	Per cent	Number	Per cent		Number	Per cent	Number	Per cent
	Sanatorium patients										
347	Adults	325	284	87.4	287	88.3	22	13	59	16	72.7
55	Children	36	35	97.2	36	100.0	19	11	57.9	11	57.9
249	Sanatorium employees	62	47	75.8	58	93.5	187	122	65.2	167	89.3
80	General population	9	5	55.5	6	66.6	71	34	47.9	62	87.3
731	Total.....	432	371	86	387	89.8	299	180	60.2	256	85.6

to the MA-100 Bovine Protein represents a community difference rather than an error in the tests made.

A further study of this question was made by correlating the X-ray findings with the results of the skin test. For this purpose the group of 6,295 individuals analyzed in table 2 was divided into two subgroups. Subgroup 1 consisted of 731 individuals tested at the Sanatorium with 0.000,5 mgm. of the MA-100 Human Protein and 0.01 mgm. of the MA-100 Timothy Protein. Subgroup 2 consisted of 5,564 school-children tested in rural Hennepin County.

The analysis of subgroup 1 is shown in table 3. In this group there were 432 individuals with X-ray evidence of tuberculosis, and, of these, 86 per cent reacted positively to the MA-100 Human Protein, while 89.8 per cent reacted positively to the MA-100 Timothy Protein. In this

group also there were 299 individuals without demonstrable X-ray evidence of tuberculosis and 60.2 per cent reacted positively to the MA-100 Human Protein while 85.6 per cent reacted positively to the MA-100 Timothy Protein. The correlations of the reactions in the various units comprising subgroup 1 may also be seen in table 3. It is interesting to note that in the patient unit and in the employee unit, in which there are some ex-patients, the percentage of positive reactors to the MA-100 Timothy Protein is greater in the group with a positive X-ray than in those without demonstrable X-ray evidence of tuberculosis. The converse is true of the well units, that is, the general population group. In this unit the percentage of positive reactors to the MA-100 Timothy

TABLE 4

X-ray findings and sputum report on 112 individuals who were positive to 0.01 mgm. of the M.A. 100 Timothy Protein only, out of 731 individuals tested with 0.000,5 mgm. of the M.A. 100 Human Protein and 0.01 mgm. of the M.A. 100 Timothy Protein

NUMBER TESTED	GROUP	POSITIVE TO TIMOTHY ONLY		X-RAY POSITIVE FOR TUBERCULOSIS		NO EVIDENCE OF TUBERCULOSIS		SPUTUM POSITIVE
		Number	Per cent	Number	Per cent	Number	Per cent	
80	General population	30	37.5	2	6.7	28	93.3	0
249	Sanatorium employees	62	24.9	13	20.9	49	79.0	3
	Sanatorium patients							
347	Adults	18	5.2	15	83.3	3	16.7	9
55	Children	2	3.6	1	50.0	1	50.0	0
731	Total.....	112	15.3	31	27.7	81	72.3	12

Protein is much greater in the group with negative X-rays than in the group with the positive X-rays.

In this same subgroup of 731 individuals there were 112, or 15.3 per cent, who reacted positively to the MA-100 Timothy Protein only. The analysis of their findings and their sputum record is shown in table 4. Considering this group as a whole, we find that 27.7 per cent had X-ray evidence of tuberculosis, while in 72.3 per cent the X-ray was considered negative for tuberculosis. The correlation of the findings of each unit is also shown in this table. It is interesting to note that in the adult patient unit the majority (83.3 per cent) of those who reacted positively to the MA-100 Timothy Protein had X-ray evidence of tuberculosis which was corroborated by positive sputum in 50 per cent of the patients.

TABLE 5

Correlation of skin test and X-ray diagnosis in 5,564 school-children in rural Hennepin County tested with the M.A. 100 Protein from the Human and Bovine Tubercle Bacillus and the Timothy Grass Bacillus

TESTING MATERIAL	NUMBER TESTED	REACTION	NUMBER +	NUMBER X-RAYED	POSITIVE FOR TUBERCULOSIS		DEFERRED		NEGATIVE FOR TUBERCULOSIS	
					Number	Per cent	Number	Per cent	Number	Per cent
I										
M.A. 100 human; 0.000,5 mgm.	3,767	(a) + to both human and timothy proteins	522	481	67	13.9	9	1.9	405	84.2
		(b) + to human only	288	21	3	14.3	1	4.8	17	81.0
M.A.100 timothy; 0.01 mgm.		(c) + to timothy only	1,383	608	7	1.2	19	13.1	582	95.7
II										
M.A.100 human; 0.000,5 mgm.	1,483	(a) + to both human and timothy protein	120	115	20	17.4			95	82.6
		(b) + to human only	102	93	24	25.8	1	1.1	68	73.1
M.A.100 timothy; 0.000,5 mgm.		(c) + to timothy only	177	0	0	0	0	0	0	0
III										
M.A.100 human; 0.000,5 mgm.	314	(a) + to both human and bovine	5	5	3	60.0			2	40.0
		(b) + to human only	42	39	6	15.4			33	84.6
M.A.100 bovine; 0.000,1 mgm.		(c) + to bovine only	1	1					1	100.0
Total.....	5,564		2,640	1,363	130	9.5	30	2.2	1,203	88.3

In the units without active tuberculosis, however, that is, in the Sanatorium-employees group and general-population group, the percentage of positive reactors to the MA-100 Timothy Protein was much larger in

those with the negative X-ray than it was in those with a positive X-ray. In this group also it is interesting to note that three of the Sanatorium employees who were ex-patients had had positive sputum at some time. It was negative, however, at the time of the test.

The results of the correlation of the X-ray findings and skin tests on the 5,564 school-children of rural Hennepin County comprising group 2 is shown in table 5. This group of children has been divided into three subgroups according to the testing material used. Subgroup 1 consists of 3,767 school-children tested with 0.000,5 mgm. of the MA-100 Human Protein and 0.01 mgm. of the MA-100 Timothy Protein. This subgroup has been further divided into three divisions. In division (a) there were 522 children who reacted positively to both testing substances. Of this number 481 were X-rayed and in 13.9 per cent the X-ray was considered positive for tuberculosis. In division (b) there were 288 children who reacted positively to the MA-100 Human Protein only. Of this number only 21 were X-rayed and in 14.3 per cent the X-ray was considered positive for tuberculosis. In division (c) there were 1,383 children who reacted positively to the MA-100 Timothy Protein only. Of this number 608 were X-rayed and the X-ray was considered positive in only 1.2 per cent.

Subgroup 2 consists of 1,483 children tested with 0.000,5 mgm. of the MA-100 Human Protein and 0.000,5 mgm. of the MA-100 Timothy Protein. This group has also been subdivided into three divisions. Division (a) consists of 120 children who reacted positively to both testing substances. Of this number 115 were X-rayed and in 17.4 per cent the X-ray was considered positive for tuberculosis. Division (b) consists of 102 children who reacted positively to the MA-100 Human Protein only. Of this number 93 were X-rayed and in 25.8 per cent the X-ray was considered positive for tuberculosis. Division (c) consists of 177 children who reacted positively to the MA-100 Timothy Protein only.

Subgroup 3 consists of 314 children tested with 0.000,5 mgm. of the MA-100 Human Protein and 0.000,1 mgm. of the MA-100 Bovine Protein. This group has been divided into the three same divisions. Division (a) consists of 5 children who reacted positively to both testing substances. We think the number is too small to be analyzed. Division (b) consists of 42 children who reacted positively to the MA-100 Human Protein only. Of this number 39 were X-rayed and in 15.4 per cent the X-ray was considered positive for tuberculosis. The number in division (c) is too small to be considered.

Is the dosage of the MA-100 Timothy Protein too large and is that why such a large percentage of individuals react positively to it? In a study of this question, 1,483 school children in rural Hennepin County were tested with the same dose (0.000,5 mgm.) of the MA-100 Human Protein and the MA-100 Timothy Protein. The results of these tests are shown in table 2. In this series 15 per cent reacted positively to the MA-100 Human Protein while 20 per cent reacted positively to the MA-100 Timothy Protein. In a further study of this question 272 individuals were tested with 0.000,5 mgm. and with 0.000,25 mgm. of the MA-100 Human Protein and with 0.01 mgm. and 0.005 mgm. of the MA-100 Timothy Protein. The group tested consisted of Sanatorium patients, both adults

TABLE 6

A comparison of the percentage of positive reactions in 272 individuals tested with the initial and one-half the initial dose of the M.A. 100 Human and Timothy Protein

GROUP	TOTAL NUMBER TESTED	HUMAN PROTEIN, 0.000,5 MGM.		HUMAN PROTEIN, 0.000,25 MGM.		TIMOTHY PROTEIN, 0.01 MGM.		TIMOTHY PROTEIN, 0.005 MGM.	
		+ Number	+ Per cent	+ Number	+ Per cent	+ Number	+ Per cent	+ Number	+ Per cent
Sanatorium patients:									
Adults	177	148	83.6	122	68.9	153	86.4	144	81.4
Children	38	34	89.5	33	86.8	35	92.1	36	94.7
Sanatorium employees	43	27	62.8	11	25.6	39	90.7	35	81.4
General population, adults	14	5	35.7	4	33.3	12	85.7	12	85.7
Total	272	214	78.7	170	62.5	239	87.9	227	83.5

and children, Sanatorium employees and a general population group of adults. The results of the tests are shown in table 6. Considering this group as a whole, we find that a larger percentage, 83.5 per cent, of individuals reacted positively to the half-strength (0.005 mgm.) of the MA-100 Timothy Protein than reacted positively (78.7 per cent) to the usual dose (0.000,5 mgm.) of the MA-100 Human Protein. The percentage of the positive reactors to the various proteins in each subgroup is also shown in table 6. In the adult-patient group the percentage of positive reactors to the half-dose (0.005 mgm.) of the MA-100 Timothy Protein is less than the percentage of positive reactors to the usual dose (0.000,5 mgm.) of the MA-100 Human Protein. In all the other subgroups, however, we find that the percentage of positive reactors to one-

half the usual dose (0.005 mgm.) of the MA-100 Timothy Protein is considerably greater than the percentage of positive reactors to the usual dose (0.000,5 mgm.) of the MA-100 Human Protein.

In this group of 272 individuals there were 36, or 13.2 per cent, who reacted positively to the MA-100 Timothy Protein only. The correlation of their X-ray findings and sputum records with the results of the skin tests is shown in table 7. Of this group, 11, or 30.6 per cent, had X-ray evidence of tuberculosis, while 25, or 69.4 per cent, had no X-ray evidence of tuberculosis. The correlations of the findings in each subgroup can also be noted in the table. It is interesting that 12, or 6.8 per cent, of the adult-patient subgroup reacted positively to the MA-100

TABLE 7

X-ray findings and sputum record on 36 individuals who reacted positively to the M.A. 100 Timothy Proteins out of 272 individuals tested with 0.000,5 mgm. and 0.000,25 mgm. of the M.A. 100 Human Protein and with 0.01 mgm. and 0.005 mgm. of the M.A. 100 Timothy Protein

NUMBER TESTED	GROUP	POSITIVE TO THE TIMOTHY PROTEIN ONLY		X-RAY EVIDENCE OF TUBERCULOSIS		NO X-RAY EVIDENCE OF TUBERCULOSIS	
		Number	Per cent	Number	Per cent	Number	Per cent
	Sanatorium patients:						
177	Adults	12	6.8	9	75	3	25
38	Children	2	5.2	1	50	1	50
43	Sanatorium employees	14	32.5	0	0	14	100
14	General population	8	57.0	1	12.5	7	87.5
272	Total.....	36	13.2	11	30.6	25	69.4

Timothy Protein only, and in 9, or 75 per cent, of this number the X-ray was considered positive for tuberculosis. According to our records, 5 of the 9 had had positive sputum at some time. In the Sanatorium employee and general-population groups, however, we find that the majority of those who reacted positively to the MA-100 Timothy Protein only were without demonstrable X-ray evidence of tuberculosis.

How sensitive and how specific are the various MA-100 Proteins? In the study of this question 104 proved tuberculous individuals were tested with Dorset's Old Tuberculin and the MA-100 proteins from the human, bovine and avian tubercle bacillus, the timothy-grass bacillus and the lepra bacillus, in 9 different dilutions ranging in testing doses from 0.000,5 mgm. to 0.000,001 mgm. as follows:

0.05 cc. = 0.0005 mgm.
0.05 cc. = 0.00025 mgm.
0.05 cc. = 0.0001 mgm.
0.05 cc. = 0.00005 mgm.
0.05 cc. = 0.000025 mgm.
0.05 cc. = 0.00001 mgm.
0.05 cc. = 0.000005 mgm.
0.05 cc. = 0.0000025 mgm.
0.05 cc. = 0.000001 mgm.

We began these tests by giving the patient an injection of the weakest dilution, that is, 0.000,001 mgm. of each testing substance so that he received six injections at the same time. If there was no positive reaction at the end of 48 hours the procedure was repeated with the next stronger dilution and so on until a positive reaction, that is, an induration of 5 x 5 mm. or more at the end of 48 hours was obtained with any dilution

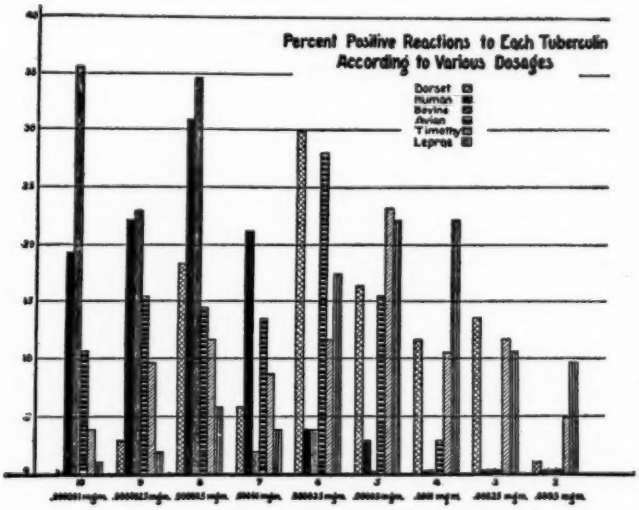

CHART 1

of any one of the testing substances. At that time further tests with that particular substance on that particular patient were discontinued. This method was followed with all the testing substances until a positive reaction was obtained or until the maximum dose was reached.

The results of the study are shown in chart 1 which compares the percentage of positive reactors to each testing substance in each dilution. In studying this chart it is interesting to note that in dilutions of 0.000,001 mgm. Dorset's Old Tuberculin was the only testing substance to which all of the 104 tuberculous individuals failed to react. Also that all of the 104 patients reacted to 0.000,025 mgm. or less of the MA-100 Bovine

Protein, and to 0.000,05 mgm. or less of the MA-100 Human Protein, and to 0.000,1 mgm. or less of the MA-100 Avian Protein. One patient failed to react to all of the doses of Dorset's Old Tuberculin and five patients failed to react to all of the doses of the MA-100 Timothy Protein and six patients failed to react to all of the doses of the MA-100 Lepra Protein.

In analyzing these results, one must remember that the usual dose of Dorset's Old Tuberculin is 0.01 mgm. rather than 0.000,5 mgm. which is the maximum dose used in this study. Possibly if Old Tuberculin had been prepared with that (0.01 mgm.) as the final dose, the results might have been very similar to those obtained with the MA-100 Human Protein. Also it is apparent that the strengths of the MA-100 proteins are as follows: Bovine, Human, Avian, Timothy and Lepra. Thus it is evident that Smith and Morris were correct in establishing a graduated scale of doses for the MA-100 proteins from the Bovine, Human and Avian tubercle bacillus and the Timothy Grass Bacillus as follows: MA-100 Bovine Protein, 0.000,1 mgm.; MA-100 Human Protein, 0.000,5 mgm.; MA-100 Avian Protein, 0.001 mgm.; MA-100 Timothy Protein, 0.01 mgm. No type specificity was noted even in dilutions of 0.000,001 mgm. This suggests that if type specificity is to be attained it can only be through purification of the tuberculoprotein.

COMMENTS

A study of the question: Are the MA-100 proteins specific or is there a protein substance common to all acid-fast bacilli, which, if given in the proper dose, will elicit the same general type of reaction as that produced by Old Tuberculin?, as analyzed in tables 2, 3, 4, 5, 6, and 7, indicates (1) that a greater percentage of individuals, be they patients with positive sputum and positive X-ray or Sanatorium employees or school-children, react positively to 0.01 mgm. of the MA-100 Timothy Protein than to 0.000,5 mgm. of the MA-100 Human Protein. (2) Also, in that group of school-children who were tested with the same testing dose (0.000,5 mgm.) of the two proteins, a larger percentage of individuals reacted positively to the MA-100 Timothy Protein than reacted positively to the MA-100 Human Protein. (3) In the adult patient group a high percentage of those, who reacted positively to the MA-100 Timothy Protein only, have X-ray evidence of tuberculosis. (4) In the other groups consisting of Sanatorium children, Sanatorium employees, nurses and school-children, the percentage with X-ray evidence of tuberculosis is much lower in those, who reacted positively to 0.01 mgm. of the MA-100

Timothy Protein only, than in those who reacted positively to the MA-100 Human Protein only or to both the testing substances.

We believe these facts indicate (1) that the MA-100 proteins cannot be type-specific and that there must be a protein substance common to all acid-fast bacilli which is just as effective in eliciting an allergic response if the proper dose is used as is the protein obtained from the human tubercle bacillus or (2) that what we call the *tuberculin reaction* represents an allergic response to sensitization by any acid-fast bacillus, including the timothy-grass bacillus.

This raises the question of whether man can be sensitized by the timothy-grass bacillus even though it is not pathogenic for him. But what do we mean by the phrase "is not pathogenic for him?" Do we mean that it will not produce a pathological implantation or that it will not produce progressive disease? In that connection Long and Vorwald (4) report some histological activity in the testes of a guinea pig following inoculation with various acid-fast bacilli including the smegma and timothy-grass bacillus. The reaction to these latter two bacilli was temporary and at the end of four weeks had almost entirely subsided. Also various authors, including Frey and Hagan (5), and Hastings, Beach and Thompson (6), and Daines and Austin (7), call attention to the fairly large percentage of "no lesions" or "skin lesion" reactors in cattle. From numerous studies these authors are of the opinion that some other mycobacterium besides that of tuberculosis is the cause of the tuberculin reaction in these cattle. Furthermore, Hastings, Beach and Thompson (6) state, "It was necessary at the beginning of the eradication movement to consider every reacting animal a tuberculous one. It seems proper to ask whether this policy should be continued." Has the control of tuberculosis in man progressed far enough to ask whether all of the positive reactions to Old Tuberculin or to the protein of any acid-fast bacilli are due to infection by the *Mycobacterium tuberculosis?* May not some other mycobacterium be the cause of the tuberculin hypersensitiveness in man or in childhood at least, even though it may be only a transitory reaction as well as in cattle?

CONCLUSIONS

1. The MA-100 Human Protein in dilutions of 0.000,5 mgm. is stable for one year at least.

2. The mercurial preservative, known to the Mulford Laboratories

as No. 186, when used in dilutions of 1–5,000 produces a false-positive reaction and its further use is not warranted.

3. Smith and Morris were correct in establishing a graduated scale of doses for the MA-100 Proteins from the human, bovine and avian tubercle bacillus and the timothy-grass bacillus as follows: MA-100 Bovine Protein, 0.000,1 mgm.; MA-100 Human Protein, 0.000,5 mgm.; MA-100 Avian Protein, 0.001 mgm.; MA-100 Timothy Protein, 0.01 mgm.

4. Dorset's Old Tuberculin and the MA-100 Proteins from the human, bovine and avian tubercle bacillus and from the timothy-grass bacillus and the lepra bacillus are not type-specific even in dilutions of 0.000,001 mgm.

5. If type-specificity is to be attained, it can only be through further purification of the tuberculoprotein.

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THE VIABILITY OF TUBERCLE BACILLI IN TISSUES AND SPUTUM PRESERVED IN VITRO[1]

C. B. VIDAL

It is well known that tubercle bacilli differ in many respects from other microörganisms and even among themselves in so far as the three pathogenic species, human, bovine and avian tubercle bacilli, are concerned. Their survival, likewise, under various conditions presents a problem that depends upon the number present as well as the individual resistance of the particular strain under consideration. Again, suitable test methods adapted to extensive investigation have not been available until within recent years (1) (2) (3), so that most of the earlier trials were concerned only with the results obtained on relatively poor nutrient media suited alone to growing large numbers of bacilli. The use of the guinea pig as test for economic reasons, though available, was restricted to limited studies, and so such information which is available on the survival of tubercle bacilli *in vitro* in tissues and excreta is scattered and rather inadequate for formulating practical conceptions.

With the development of culture methods by Corper and his colleagues, for growing small numbers of tubercle bacilli, it appeared desirable to study the survival of tubercle bacilli under various conditions, such as might be encountered in the regular routines of life and in the light of the effect on different amounts of the bacilli present.

Since there are many factors involved in a study of this type which are hardly pertinent to presenting the actual facts of experiment and since the subject itself does not warrant an elaborate detailed report of all the experiments performed to obtain the practical data to be recorded, only such tabulations and information will be reported herein that will support the important and pertinent conclusions drawn from such experiments. The general plan of the experiments was to obtain specimens of tissues (lung, liver, spleen and kidney) experimentally implanted with different amounts of tubercle bacilli, as well as natural tuberculous materials, such as sputum, and to determine the survival of the bacilli contained therein under different temperature conditions: ice-chest (slightly above the

[1] From the Research Department, National Jewish Hospital, Denver, Colorado.

freezing point of water (2°C.)), room temperature (varying between 20° to 25°C.), and incubator temperature (37°C.). Obviously, as has been pointed out by Corper previously (4), changes in acidity, due to fermentation or putrefaction, and to autolysis of tissues at different temperatures and especially at the higher temperatures, are pertinent to the final outcome of the tests. When materials could be obtained aseptically, the factors of fermentation and putrefaction could be ruled out; but with natural specimens, such as sputum, they played no small part in the final result but were obviously retarded at the lower temperatures. Yet, since this study was concerned with duplicating such conditions as would be encountered in practice, it is presented in this light, and the findings accordingly speak for themselves, unencumbered by theoretical evaluation as is evident in certain disinfection reports. The explanations that will be noted are involved in multiple factors, including autolysis, reaction (H-ion concentration), moisture, temperature, etc.

Some of the conditions for the prolonged survival of tubercle bacilli are well discussed in a recent paper by Corper and Cohn on twelve-year-old cultures of tubercle bacilli (5).

In order to gain an insight into the significance *in vitro* of the organ (6), the amount of contained bacilli and the temperature of storage, a series of three rabbits was given intravenous injections of 1.0, 0.01, and 0,000,001 mgm. each, respectively, of a virulent strain of human tubercle bacilli (Gluckson), or of a bovine glycerophilic strain of tubercle bacilli; and the organs, namely, lung, liver, spleen and kidney, were removed within the first week after intravenous injection. Pieces of the aseptically removed organs were placed in sterile specimen bottles stoppered with paraffined cork stoppers and these were placed in a tin can covered with a lid and kept under the condition designated under the data recorded in table 1.

The results recorded in table 1 for bovine tubercle bacilli in rabbit tissues show that these bacilli lose their viability in such tissues at room temperature (20°C.) within five days; while at refrigerator temperature (about 2°C.) viability, as determined by culture methods capable of discerning small numbers of viable bacilli, is not completely destroyed until after ten to thirty days, dependent upon the tissue containing the bacilli. The liver or lung tissues *in vitro* apparently destroy the bacilli slightly more rapidly than the spleen or kidney tissues. The results with human tubercle bacilli were not tabulated because, in general, the findings conformed to the results with the bovine bacilli, except that loss of viability

TABLE 1

Viability of bovine tubercle bacilli in the organs of the rabbit kept in vitro under different temperature conditions

AMOUNT OF FINE SUSPENSION OF BACILLI GIVEN INTRAVENOUSLY TO RABBIT	ORGAN USED AS TEST	CONTROL CULTURE RESULTS	TEMPERATURE OF PRESERVATION†	CULTURE RESULTS AFTER INTERVALS DESIGNATED					
				1 day	5 days	10 days	20 days	1 month	2 months
			°C.						
1.0 mgm.	Lung	2*	2	2	2	6	8	12	0
			20	2	0	0	0	0	0
	Liver	2	2	2	4	8	10	0	0
			20	2	0	0	0	0	0
	Spleen	2	2	2	2	2	4	10	4
			20	2	0	0	0	0	0
	Kidney	2	2	2	2	2	2	6	0
			20	2	0	0	0	0	0
0.01 mgm.	Lung	2	2	4	2	4	4	0	0
			20	4	6	0	0	0	0
	Liver	4	2	4	4	4	0	0	0
			20	4	0	0	0	0	0
	Spleen	4	2	4	4	4	0	0	0
			20	4	0	0	0	0	0
	Kidney	4	2	4	2	4	4	4	0
			20	4	0	0	0	0	0
0.000,001 mgm.	Lung	4	2	6	0	0	0	0	0
			20	4	0	0	0	0	0
	Liver	4	2	6	4	0	0	0	0
			20	4	0	0	0	0	0
	Spleen	4	2	4	4	4	8	0	0
			20	4	0	0	0	0	0
	Kidney	4	2	6	4	4	0	0	0
			20	0	0	0	0	0	0

* The numeral indicates the earliest interval in weeks in which the planted organs revealed positive growths on the culture mediums. The cultures were obtained by the sulphuric-acid-potato-cylinder method (Arch. Pathol., 1929, vii, 835).

† The temperature recorded is only approximately accurate.

occurred slightly earlier in each case than with the bovine bacilli. This conforms to the fact, previously established in this laboratory and by other observers, indicating the greater resistance of bovine bacilli as a rule to physical and chemical reagents *in vitro*.

TABLE 2

The viability of human tubercle bacilli in positive tuberculous sputa maintained at different temperatures

DEFINITELY POSITIVE SPECIMENS USED	TREATMENT ACCORDED SPUTUM	TEMPERATURE OF PRESERVATION	RESULTS RECORDED WHEN POSITIVE CULTURES WERE OBTAINED									
			Control	1 day	5 days	10 days	1 month	2 months	4 months	6 months	12 months	18 months
		°C.										
1. Sputum	Natural	2	2*	2	2	6	4	4	8	6	6	0
		20		4	4	8	10	0	0	0	0	0
2.† Sputum	Natural	2	2	2	2	4	4	4	4	4	4	0
		20		2	4	4	6	6	12	0	0	0
Empyema fluid	Natural	2	4	4	4	8	4	6	8	10	0	0
		20		4	4	4	8	0	0	0	0	0
4.‡ Sputum	+0.9% NaCl	2	4	4	4	4	6	6	8	12	0	0
		37		4	6	0	0	0	0	0	0	0
	+4% glucose in 0.9% NaCl	2		4	4	4	4	4	0	0	0	0
		37		4	0	0	0	0	0	0	0	0
	+4% glucose +37.5% glycerol in NaCl	2		4	4	6	0	0	0	0	0	0
		37		6	0	0	0	0	0	0	0	0

* The numeral recorded indicates the number of weeks in which macroscopic growth made its first appearance on the culture medium.

† The results of the findings with the third sputum are not recorded since they differed only slightly from those with sputa 1 and 2.

‡ The findings with sputum 5 closely paralleled those with sputum 4, and are therefore not recorded.

In order to determine the effect of residence in the ice-chest or at room temperature upon human tubercle bacilli in sputum, three positive sputa and a positive empyema fluid were cultured by the sulphuric-acid-potato-cylinder method with the results recorded in table 2. In addition, two sputa were studied at ice-chest and incubator temperature after the

addition of an equal volume of sterile physiological saline (0.9 per cent sodium chloride) solution, an equal volume of sterile saline containing enough glucose to give a final 4 per cent concentration, or an equal volume of sterile saline containing enough glucose to give a final 4 per cent concentration and pure glycerol to give a final 37.5 per cent concentration. These tests were added because of a report published recently (7) that the bacilli in sputum were able to multiply under such conditions at incubator temperature.

It is obvious that the findings recorded in table 2 on the viability of the human tubercle bacilli contained in positive sputa preserved under different conditions at various temperatures, cannot be quantitatively exact because a sputum, positive microscopically, is to be considered as heavily laden with bacilli as has been previously pointed out (1). However, the data permit some valuable practical interpretation in that, even at room temperature, some of the human tubercle bacilli contained in sputum may remain viable, under proper conditions taken to avoid the effect of drying and light, for as long as four months at ice-chest temperature; the viability of some of the bacilli may even be preserved up to as long as twelve months. Sputum, therefore, does not appear to be as detrimental to the contained bacilli as tissues, although in making this deduction, it is well to remember that a positive sputum may be more heavily laden with bacilli than the organs of the rabbit given as much as one milligram of bacilli intravenously, and the phenomenon noted may well be explained on the basis of the well-established fact that large numbers of tubercle bacilli can survive detrimental physical and chemical influences far better than smaller numbers of bacilli.

However, it is clear from the findings recorded in table 2 that attempts to grow tubercle bacilli in sputum to which has been added 4 per cent glucose, with or without 37.5 per cent glycerol, are futile, since these reagents act decidedly detrimentally on the contained bacilli at incubator temperature. It appears that the action of the glycerol in this concentration (37.5 per cent) is directly detrimental while that of the glucose may be indirect only, and due to the formation of fermentation products (acid, etc.) when added to an unsterilized sputum specimen (the evolution of fermentation gases and change in reaction noted during the course of the tests would appear to verify these suggestions).

In view of the fact that various other microörganisms and spores have at times been preserved by keeping them in animal organs such as the spleen of the mouse or guinea pig or in such organs placed on filter paper,

an experiment was planned to determine whether tubercle bacilli could be preserved in this manner. For this purpose the lung, liver, spleen and kidney tissue of rabbits, given intravenous injections of 1.0, 0.001 and 0.000,001 mgm. of human and bovine tubercle bacilli, were rubbed into small sterile pieces of pure filter paper; and they were preserved in small bottles, some without the addition of moisture and some containing in each bottle a few cubic centimetres of sterile neutral 0.9 per cent sodium-chloride solution. These papers were kept at ice-chest, room temperature and incubator temperature; and, while the bacilli remained viable in these tissues at ice-chest temperature longer than at room temperature, and longer at room temperature than at incubator temperature, they did not remain viable for a greater length of time than they did in the organs recorded in table 1. The moist papers proved more satisfactory in preserving viability than the dry filter papers. Contaminations and irregularity in the results with the filter papers were conspicuous also and would not appear to favor such a method of preservation. Since the initiation of this work, Corper and Cohn (5) have found that the bacilli can best be preserved in the original broth cultures protected against drying and buffered to maintain a reaction approximating a neutral reaction of pH 7.0.

SUMMARY

Human and bovine tubercle bacilli contained in rabbit tissues (lung, liver, spleen and kidney) following intravenous injections of amounts (in fine suspension) ranging from one to one-millionth milligram lose their viability in these tissues kept under sterile conditions *in vitro* at room temperature (20°C.) within five days; while at refrigerator temperature (about 2°C.) viability, as determined by delicate culture tests, is not completely lost until after ten to thirty days. In liver or lung tissues loss of viability occurs a little earlier than in the spleen or kidney, and bovine bacilli are slightly more resistant to this effect than human tubercle bacilli, in conformity with previous observations by Corper and others, who noted a greater resistance of bovine bacilli to detrimental physical and chemical influences in general. The viability of tubercle bacilli in tissues (lung, liver, spleen and kidney of the rabbit) was not preserved any longer on sterile strips of filter paper (preserved dry or moist) than they were in small pieces of the organs kept under the same temperature conditions. The dry paper proved less satisfactory for preserving the viability of the bacilli than did moist papers. Preservation in broth

cultures or in buffered nutrient solutions as recommended by Corper and Cohn would appear more satisfactory. Human tubercle bacilli in sputa positive microscopically were found to be viable at room temperature (20°C.) for as long as four months, provided the detrimental effects of drying and light were obviated, and at refrigerator temperature (2°C.) some of the bacilli were still alive after twelve months. It would appear from this that sputum does not affect the viability of tubercle bacilli as detrimentally as do tissues; a positive sputum, is, however, more heavily laden with bacilli than were the tissues tested and this may in part explain the marked differences noted.

It appears futile to attempt to grow tubercle bacilli in native sputum directly with or without the addition of glucose or glycerol, especially when the bacilli contained therein are few in number and contaminating microörganisms are not destroyed beforehand.

Note: The author is grateful to Ray Stoner for assisting with the experimental part of this report.

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TUBERCULOSIS AND MENTAL DISEASE

A Tuberculin Survey in a State Hospital

EMIL BOGEN,[1] ESTHER BOGEN TIETZ[2] AND MAJOR FRANK GRACE[2]

The excessive mortality from pulmonary tuberculosis in hospitals for mental diseases has been frequently pointed out (1) and has formed the basis for a number of speculations concerning its significance. Thus, the fact that patients with dementia praecox so frequently die of tuberculosis has led some writers to consider the "schizoid type" as "constitutionally predisposed" to phthisis (2), while others maintain that dementia praecox may be itself a peculiar manifestation of tuberculous infection (3). The lowered resistance to the disease resulting from the unfavorable conditions of incarceration in insane asylums and other institutions (4) and the increased exposure to massive infection and reinfection in such surroundings have also been arraigned (5). An objective analysis of the facts concerned may lead to a better understanding of the relative importance and adequacy of the explanations offered.

At the Longview State Hospital for Mental Diseases in Cincinnati, Ohio, with an average patient population of about 2,200, there has been a tuberculosis mortality rate in the past few years of 0.7 per cent, more than ten times that of the state in which it is located. Even higher death-rates from this cause are found in many of the mental hospitals in other communities, and similar conditions are also present in many penal institutions.

Clinical Tuberculosis

Clinical examination of all of the patients in the institution led to the recognition of 68 patients with pulmonary tuberculosis. This figure, about four times the annual number of deaths from this cause in the institution, compares favorably with the number of cases recognized in other institutions in the state, but should be increased by more thorough examinations utilizing laboratory and X-ray criteria more freely. Un-

[1] Olive View, California.
[2] Longview Hospital, Cincinnati, Ohio.

fortunately, adequate facilities for the isolation of all of these patients were not available, and they were found scattered in more than half a dozen different wards.

TABLE 1

Clinical tuberculosis in Longview patients

	PATIENTS EXAMINED	CLINICALLY TUBERCULOUS	PER CENT
Sex:			
Male	1,155	29	2.5
Female	1,120	39	3.5
Total	2,275	68	3.0
Age:			
Under 40 years	1,138	46	4.0
40 years and over	1,137	22	1.9
Duration of hospitalization:			
Under 1 year	465	7	1.5
1–5 years	635	19	3.0
5 years and over	1,175	42	3.5
Width-length index:			
Over 180	951	27	2.8
Under 180	1,170	37	3.2
(Not measured)	154	4	
Diagnosis:			
Senile	224	4	2
Syphilitic	253	6	3
Alcoholic	92	3	3
Manic depressive	396	13	3
Dementia praecox	638	24	4
Paranoid	192	6	3
Psychoneurotic	110	5	5
Feeble-minded	185	4	2
Miscellaneous	185	3	2

Only 10 per cent of the tuberculous patients had been admitted to the Longview Hospital since the beginning of the last year, while more than twice that proportion of the other patients had been so recently admitted, and the incidence of the disease appeared to increase with the duration of confinement in the institution. Nevertheless, the tuberculous patients averaged less than thirty-five years of age, while the average age of all patients in the institution is more than forty.

The incidence of the disease among the various groups of mental disturbances was lower among the senile and syphilitic groups, and higher among the patients with the so-called "constitutional psychoses," but this difference corresponded with the difference in the duration of stay in the institution of the two groups. Contrary to expectation, the patients with tuberculosis in this institution do not appear to be underweight, probably as a result of the special efforts made to secure adequate nutrition, especially on the male tuberculosis ward. The dementia-praecox patients showed little more tuberculosis than did those with manic-depressive psychoses, although their nutrition did not appear to be as well maintained.

Width-Length Indices

The relative width of the bony pelvis gives one of the simplest indices of body build, since it is not affected by differences in nutrition or in chest measurements resulting from disease (6). This measurement increases with age, more markedly among the women patients than among the men, but does not seem to be greatly affected by multiparity. Thus the tuberculous patients were, on the average, slightly narrower than the entire patient population at Longview, but little different than the other patients of the same age (7). Similarly, the dementia praecox patients appear narrower than do those with manic depressive psychoses, just as the latter are still narrower than the patients with senile psychoses, but when only patients in the same age-group are compared, the differences in body build between the various types of mental disease, as shown by this index, vanishes.

Examination of the cases recognized as suffering from clinical tuberculosis in the Longview Hospital for Mental Diseases, then, shows that the incidence of such disease increases with the length of stay in the institution, but is not appreciably affected by body build or type of psychosis. Since tuberculosis is found more in the younger patients, this cannot be ascribed to the decrease in the incidence of the disease in recent years, but appears directly attributable to the contraction of the infection and the development of the disease after admission to the institution; in other words, the disease develops, not as a result of the mental disease *per se*, or as its cause, but from the conditions of confinement and exposure to infection resulting therefrom.

Tuberculin Tests

In view of the difficulty of recognizing early tuberculosis even in those able to describe early symptoms, and the doubled difficulty of eliciting such data in the mentally diseased, it was decided to test the entire hospital population for tuberculin skin sensitivity, thus obtaining an idea of the relative incidence of the infection in the different groups, which may be, of course, quite different from the presence of actual clinical tuberculous disease, but is an essential factor in its production and might indicate where to look for manifest phthisis. For safety and convenience in dealing with the unruly patients, the Pirquet technique was used throughout, scarifying through Old Tuberculin with the Pirquet chisel on the flexor surface of the left forearm, and reading in forty-eight hours, with a check reading again in five days. No systemic reactions were observed, but in a few instances the local lesions were accentuated by scratching or biting the area tested by the psychotic patients. It is recognized that a few positives, missed by the Pirquet technique, might be revealed by larger doses of tuberculin given intracutaneously, but it is not believed that the additional reactors so produced would make any significant differences in this study.

Altogether, more than 2,200 patients were tested, together with a number of nurses, attendants and other employees. Nearly a quarter of all of the tests were read as negative, showing little or no response to the injection, and a somewhat larger number were recorded as doubtful, showing only a small reaction, which would, however, probably be interpreted as positive by many workers.

There were marked differences in the incidence of the reactions on different wards, more than a quarter of the patients on the admitting wards being completely negative, while on the wards containing active cases of the disease less than half that number failed to react, and less than 20 per cent of the patients on the admitting wards showed a strongly positive reaction, as compared to more than twice that number on the remaining wards, and an even higher proportion on the wards in which patients with active tuberculosis were clinically recognized.

The differences in reactions, according to the length of time that the patients had been at Longview, are just as striking. More than a quarter of the patients admitted to Longview during the past five years gave negative tests, while, of those admitted prior to that time, only one-sixth are now negative to this test. The increase in positive tuberculin

TABLE 2

Patients with negative tuberculin tests

	NUMBER OF PATIENTS	PER CENT
Sex:		
Male	225	20
Female	246	22
Age:		
Under 40 years	191	17
40 years and over	234	20
Duration of hospitalization:		
Under 1 year	125	27
1–5 years	143	23
5 years and over	203	17
Diagnosis:		
Senile	64	29
Syphilitic	44	17
Alcoholic	20	22
Manic depressive	86	21
Dementia praecox	136	21
Paranoid	46	24
Psychoneurotic	11	10
Feeble-minded	33	18
Miscellaneous	34	18

TABLE 3

Comparison of manic depressive and dementia praecox patients

	MANIC DEPRESSIVE	DEMENTIA PRAECOX
Sex:		
Male	147	360
Female	249	278
Age:		
Under 40 years	165	508
40 years and over	231	130
Duration:		
Under 1 year	85	77
1–5 years	148	282
5 years and over	163	279
Width-length index:		
Over 180	198	240
Under 180	198	393
Width-length index in patients aged 30–40:		
Over 180	32	57
Under 180	73	122

tests with increase in the duration of stay in the institution is marked among both the men and the women, and can be noted clearly even in the case of the patients suffering from any one disease, as among the dementia-praecox patients. The mere increase in age of these patients during this time is not responsible for this increased incidence of positive tests, because new admissions average a somewhat higher age-incidence than do the surviving population of the hospital, and examination of the patients of various ages shows little tendency to increase in positive reactions among the older groups.

The fact that the attempt at segregation of tuberculous patients at this institution, admittedly inadequate as it is, during the past few years has been accompanied by a marked drop in the mortality rate from this condition might be interpreted as confirmatory of this interpretation, and as presaging even greater success if the policy of segregation of active cases is more thoroughly carried out.

SUMMARY

The death-rate from tuberculosis in institutions for the care of patients with mental diseases is extraordinarily high. A tuberculin survey of a large state hospital, comprising more than two thousand patients, shows that tuberculous infection increases among these patients according to the length of their stay in the institution, and indicates that many of them contract the infection, as well as the disease, after their admission. Comparison of the data for the different types of mental diseases indicates that the marked differences in the tuberculosis morbidity and mortality rates among them may be, for the most part, ascribable to differences in duration of stay in the institutions, and consequent exposure to infection and disease, rather than to any immunological mechanism. The differences in the physical appearance of patients with different mental diseases appears to be partly due to nutritional differences, resulting from, rather than predisposing to, the disease, together with the marked differences in age-grouping encountered between the different groups studied. The doctrine of "constitutional types" underlying predisposition to mental diseases and to tuberculosis is not supported by the data here presented.

Thanks are due to Dr. Baber, superintendent of the Longview State Hospital, for wholehearted coöperation in this investigation, to the entire nursing staff and attendants at the institution for their devoted and efficient aid in the progress of the work, and particularly to the thousands of patients whose interest and coöperation formed such an unexpected and delightful feature of the study.

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THE EFFECT OF MODERATELY LARGE DOSAGE OF VIOSTEROL ON TUBERCULOUS CHILDREN[1]

H. G. PONCHER AND B. M. GASUL

The mineral metabolism in tuberculosis has been a subject of great interest to those concerned with the therapy of the disease. Recent data available on this subject are excellently summarized by Wells and Long (1). These authors offer the following general conclusions in regard to our present knowledge of calcium metabolism in tuberculosis:

> The theory that tuberculosis is accompanied by, and perhaps dependent upon a demineralization, and especially a loss of calcium from the body, has not been supported by the best controlled investigations. There has been no acceptable evidence that there is any significant decrease in the amount of calcium in either the blood or the tissues in tuberculosis. Neither has it been shown that the amount of calcium in the blood and tissues can be measurably increased, at least more than momentarily by feeding calcium compounds of whatever sort in tuberculosis or in any other condition, in which the blood calcium is not appreciably below normal.

The reports of metastatic calcification following the experimental use of large doses of irradiated ergosterol however presented another problem. Here, the hypothetical therapeutic ideal is not concerned with normal calcium metabolism but in the creation of a nontoxic hypercalcaemia, so that more than the usual amount of calcium would be available for calcification of the tuberculous lesion. In some of the first experimental work on the laboratory animal calcium depositions in various organs and tissues were observed with the use of massive doses of irradiated ergosterol (2). Since calcification is assumed to be favorable termination of certain types of tuberculous lesions, various investigators sought to induce selective calcium deposition in experimental tuberculous lesions in animals. Spies (3) observed that the caseous lesions of acute and chronic experimental bovine tuberculosis in rabbits calcify more extensively in animals which have received large doses of irradiated ergosterol. Simmonet and Tanret (4) showed by chemical analysis that large doses of

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irradiated ergosterol increased the calcium content of normal and tuberculous lung tissue. Levaditi and Li (5) found that experimental chronic human testicular and pulmonary tuberculous lesions in rabbits' tissues can be made to calcify under the influence of massive, but subtoxic doses of irradiated ergosterol (5 mgm. per kilo). No heterotopic calcification occurred in other organs on the doses employed. Policard, Paupert-Ravault and Barral (6) reported calcium deposition in caseated tubercles in tuberculous guinea pigs under the influence of irradiated ergosterol only when the dose is 5 mgm. or higher. This amount however caused deposition of calcium in normal organs or tissues. Walker and Spies (7) found that repeated massive doses, 36 minims of irradiated ergosterol (having a codliver-oil coefficient of 10,000 X) in 3 doses over a period of four days caused extensive calcification within the caseous lesions of guinea pigs with acute bovine tuberculosis. Heterotopic calcification was also observed in normal organs. Two healthy animals were given 75 minims in 4 doses over a period of 5 days but they found calcification more marked in those animals with tuberculosis.

Jampolis and Witt (8) injected 2 groups of guinea pigs intramuscularly with a virulent culture of human tubercle bacilli. One group was given a preliminary injection of a known avirulent strain of human tubercle bacilli 6 weeks before the injection of the virulent culture. This was done in an attempt to simulate tuberculosis as it occurs in the human being. Irradiated ergosterol, ten times the strength of viosterol (250 D), was administered orally and the effect on calcification of the lesions was studied. The following results were noted: Spontaneous calcification did not occur in the tuberculous animals which received no irradiated ergosterol. Those which received a daily dose of 0.1 to 1 cc. of the concentrated solution of irradiated ergosterol showed hypercalcaemia and hyperphosphotaemia, and calcification of the caseous tubercles. If the therapy was not prolonged over two months, calcification of normal tissue was not observed. However, when the control and infected animals were given daily doses of 0.5 to 1 cc. of the concentrated solution for more than two months, calcification was noted in the walls of the renal vessels and tubules. A very significant observation was made in the group which had been previously sensitized by the avirulent bacilli. No definite calcification occurred in these animals on the same doses of irradiated ergosterol which caused calcification in the group not previously sensitized. This raises the question of whether calcification does not take place more readily where primary tissue necrosis occurs. Accord-

ingly, the authors' conclusion that calcification of tubercles is "not merely an expression of simple tissue necrosis but rather a reparative process" is open to question. In this study the maximum daily dose of irradiated ergosterol given to the guinea pig would correspond to 300 cc. of viosterol given to a child weighing 22 pounds.

There appears to be no observation of the treatment of experimental tuberculosis in animals with doses of irradiated ergosterol that might be considered a rational therapeutic dose. In the few instances in which smaller doses have been used in experimental animal tuberculosis no specific effect on the tuberculous process has been observed (9).

Data concerning the use of irradiated ergosterol in producing calcification of the tuberculous lesion in the human being are meagre. Most of the reports have dealt in a general way with the use of irradiated ergosterol in tuberculosis or the amounts employed were too small to elicit a persistent hypercalcaemia. The instances in which calcification of the tuberculous lesion in animals was produced indicated that this could only be accomplished with the use of massive doses. In many of the reports calcification was also found in normal tissue (10). This is an undesirable effect and is outside the scope of therapeutics. Unfortunately, much of the early work on experimental tuberculosis was done before the biological method of standardization of irradiated ergosterol was adopted, so that it is not possible to judge what the comparable dose would be for the human being. If we are to interpret the findings of Spies and Walker (7) and Jampolis and Witt (8) the dose required to produce the desired effect in the human being would be very large. Kaminsky and Davidson (11) found that the oral administration of 10 to 20 drops of viosterol daily to adult patients with pulmonary tuberculosis caused a slight rise in the serum-calcium. The increase, however, had no influence upon the calcification of the pulmonary lesion in so far as could be demonstrated by the roentgenogram. Grayzel, Shear and Kramer (12) conducted a carefully controlled investigation on 18 children with bone tuberculosis, 9 of them serving as controls. All children received 2 teaspoonfuls of codliver oil daily but the treated children received 4 mgm. of irradiated ergosterol daily for the first four months and 8 mgm. daily for the succeeding 8 months (doses corresponding to a biological standard of 4 and 8 cc. of 150 D). They concluded that the addition of irradiated ergosterol to a balanced vitamine-sufficient diet had no effect on the course of bone tuberculosis. Relatively large therapeutic doses caused no toxic symptoms, observable pathological calcification or hypercalcaemia. Menschel (13) observed improvement in exudative tubercu-

lous processes and haemoptysis with moderate doses of irradiated ergosterol. No calcium and phosphorus determinations were made and the clinical observations were not adequately controlled. When the patients were given large doses of irradiated ergosterol loss of appetite and weight were noted. Crimm (14) reports no positive findings in the clinical course or X-ray appearances in 10 adult tuberculous patients who were given 15 drops of viosterol twice a day for a period of 4 months. While he found an increased calcium-phosphorus product of the serum on this therapy he was conservative in his clinical interpretation because of the small number of cases studied. In a later communication (15) he reported his observations on 15 adult patients with tuberculosis who were given a concentrated solution of irradiated ergosterol daily from periods varying from 8 to 32 days. The amount and potency of the preparation he used would correspond with about 80 cc. of viosterol daily. Definite hypercalcaemia was produced in all cases, varying from 13.8 to 17.5 mgm. of Ca per 100 cc. of serum. While conclusive data were lacking with reference to the specific effect on the tuberculous lesion, Crimm felt that irradiated ergosterol may favor fibrosis and hasten absorption of the tuberculous infiltration in pulmonic tissue when given at the proper time. From his observation he felt that a dose which would correspond to 80 cc. of viosterol for a 5-day period produces a hypercalcaemia in the vicinity of 15 mgm. of Ca per 100 cc. of serum which is compatible with the well-being of the patient. He concluded that further work was however necessary in order to determine the therapeutic value of hypercalcaemia in pulmonary tuberculosis.

From a previous investigation we had observed that very large doses of viosterol could be given over a relatively long time without hypercalcaemia (16) (Hess, *et al.*). However, when the dose was markedly increased, loss of weight was noted. This symptom is undesirable in a patient with tuberculosis. Further, in a limited number of normal and rachitic infants it was found that when we gave enough viosterol to produce a persistent hypercalcaemia, loss of appetite, muscular asthenia and vomiting were noted (17). Therefore in this investigation an amount of viosterol was adopted which was considered to be a subtoxic dose for prolonged therapy.

PLAN OF INVESTIGATION

Fifty-nine children, all contacts to tuberculosis and showing at least a definitely positive tuberculin reaction, were chosen among the patients at the Municipal Tuberculosis Sanitarium of the city of Chicago for our

investigation. Of these patients, 11 showed definite parenchymatous pulmonary tuberculosis, the rest showing either calcified lymph nodes, Ghon tubercles, enlarged noncalcified hilum lymph nodes or no definite roentgenological evidence of tuberculosis. The youngest child was 3 years of age, and the oldest sixteen. There were 3 Mexican, 13 colored and 43 white children. Twenty-nine were females and 30 were males. The preliminary blood-calcium and phosphorus were determined, and 150 drops of viosterol were given once daily for 4 months.[2] The dose of viosterol was then increased 300 drops and continued once daily for another 3 months. Blood-calcium and phosphorus were determined once a month, the blood always being taken in the morning, and stereoscopic roentgen rays were taken once a month. Thirty-five of these 59 children were then followed up for an additional 8 months during which time they received no viosterol at all.

SUMMARY OF RESULTS

1. The preliminary blood-calcium varied from 8.48 to 12.08 mgm. per 100 cc. The preliminary blood phosphorus varied from 3.01 to 6.41 mgm. per 100 cc. and the preliminary Ca x P product varied from 30.00 to 67.05 mgm. per 100 cc. of the blood.

2. The average monthly blood-calcium during this investigation varied from 9.2 to 11.2 mgm. per 100 cc.; the average blood phosphorus from 4.3 to 5.2 mgm. per 100 cc. and the average Ca x P product from 43.99 to 57.72 mgm. per 100 cc.

3. The blood-calcium at the end of the investigation varied from 9.69 to 11.24 mgm. per 100 cc.; the blood phosphorus from 4.04 to 5.86 and the Ca x P product from 40.28 to 63.17 mgm. per 100 cc. of the blood.

4. The great majority of all patients, with few exceptions, showed a slight or moderate gain in weight during the 4 months when 150 drops of viosterol was given to them.

5. Fifty per cent of our patients lost weight during the 3-month period when 300 drops of viosterol were given, and only about 30 per cent showed a slight or moderate gain in weight.

6. All patients gained weight during the 8 months when viosterol was discontinued, and this gain in the majority of cases was much greater than the gain when 150 drops of viosterol was given.

[2] The viosterol used in this investigation was supplied by Mead Johnson and Company, Evansville, Indiana.

7. The pulse-rate, appetite, number of stools, and general clinical appearance were not materially affected during this investigation.

8. No definite changes were noted in the roentgenological examination of these patients.

DISCUSSION

The dosage of viosterol employed in this investigation did not appear to have any definite effect on the course of the tuberculous process. Hypercalcaemia was not produced by doses ranging from 150 to 300 drops of viosterol daily for a period of 8 months. The advisability of using a larger dose for a shorter period of time as suggested by Crimm (15) may be considered. Further carefully controlled investigation is necessary however to indicate the value of such a procedure.

From our observation the use of relatively large therapeutic doses administered to patients with tuberculosis over a long time is not favorable. Despite the failure to produce a definite hypercalcaemia it was our impression that interference with the weight-curve that occurred is an undesirable effect. It may be that the administration of a larger dose for a short period of time will obviate this difficulty. Nevertheless we have evidence that, when hypercalcaemia is produced, symptoms such as anorexia and muscular weakness occur. While these symptoms disappear when viosterol is discontinued the desirability of hypercalcaemia with such symptoms, even as temporary sequelae, is open to question.

Our weight-charts show the great majority of all patients gaining weight moderately during the period when 150 drops of viosterol was given. Between June and September when the dose was raised to 300 drops, there is a sharp decline in the weight curve in about 50 per cent of our patients. All patients, however, gained weight when viosterol was discontinued, and this gain is much more pronounced than during the period when 150 drops of viosterol was administered. Thus patient no. 2 gained $6\frac{1}{4}$ pounds during the 4 months on 150 drops of viosterol, and lost over 5 pounds during the next 3 months when 300 drops of viosterol was given. Patient no. 3 gained $\frac{1}{4}$ pound on 150 drops of viosterol, lost $2\frac{1}{4}$ pounds on 300 drops, and gained over 7 pounds when viosterol was discontinued. Number 7 lost 1 pound on 150 drops of viosterol and gained almost 10 pounds when viosterol was discontinued. Number 8 showed a gain of 22 pounds when viosterol was discontinued. Number 45 gained $15\frac{3}{4}$ pounds on 150 drops, lost 15 pounds on 300 drops, and regained $6\frac{1}{2}$ pounds when viosterol was discontinued.

CONCLUSION

The advisability of using moderately large doses of viosterol in children with tuberculosis over a long period is questioned. No conclusion can be drawn as to the specific effect on the course of the disease or the progress of the lesion, as our data are insufficient. It can be definitely stated however that the secondary effects of such therapy do not appear to be favorable to the patient. Such a statement has no bearing on the use of ordinary doses of viosterol to provide adequate doses of vitamine D to the diet of patients with tuberculosis.

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A DIETARY TREATMENT FOR TUBERCULOSIS

I. Results in Bone and Joint Tuberculosis[1]

HENRY STEMPA

I should like to call attention to a dietetic treatment of tuberculosis that we have been using during the last four years at Cedar Crest Sanatorium, Hartford, Connecticut. Although the question of the amount of salt ingested by the patient occurs frequently and importantly in the following discussion, the treatment under consideration has nothing to do with the "salt-free-diets" of which we have heard so much in recent years. Before telling of the results of this treatment let me relate briefly of what the diet consists. It is based on the discovery of Setti (1) and his followers that "animals fed upon a rich diet but on a diet poor in vitamines and minerals, increased the virulence of tubercle bacilli injected into their blood or abdominal organs, but that tubercle bacilli injected into animals fed with sufficient vitamines and minerals lost much of their virulence."

The new treatment is simply an attempt at supplying the necessary vitamines and minerals in such quantities as will enable the patient's blood to lessen the virulence of the tubercle bacilli, and thus make it easier for his defense powers to destroy the invading germs.

Before proceeding to give the details of this treatment in all my cases, I shall mention our results with the method in the treatment of bone and joint tuberculosis. For the cure of this disease two things are necessary: the offending germ must be destroyed, and an increased amount of calcium must be brought to the site of the disease. As has been already stated, the administration of foods containing vitamines and minerals, especially calcium, in abundance will check the tubercle bacillus, but the ingestion of excessive amounts of sodium chloride will lessen the amount of calcium in the blood, which will therefore fail to deposit a sufficient amount of lime to build up the broken-down bone at the site of the tuberculous lesion, and the absence of the necessary vitamines will

[1] From the State of Connecticut Tuberculosis Sanatorium, Cedar Crest, Hartford, Connecticut.

increase the disease-producing and destructive powers of the tubercle bacilli.

On the other hand, the exclusion of all sodium chloride from the dietary leads to frequent digestive disturbances that weaken the patient and his resistance even to faintly pathogenic tubercle bacilli. Therefore all our patients on this dietary treatment receive two grams of salt every day.

"Why fix on two grams?" The answer is that all students of nutrition agree that the average person takes more salt than he needs. Adults everywhere ingest 20 or 30 or more grams of salt every day.

The great authority on nutrition, von Noorden, (2) states: "We eat too much salt, and we would be better off if we decreased the daily intake of salt. When one lives on a high salt diet he decreases the proportion of calcium in his blood and this lowers his resistance."

On the other hand, Vincent (3) and others claim that "The complete withdrawal of salt is followed by the appearance of certain symptoms, chief of which are: lassitude, weakness, dyspepsia, anorexia, and cramps. These symptoms are promptly relieved by restoring the usual allowance of salt."

Even on a "low" salt diet, I have had several patients, who showed such symptoms as anorexia, nausea, dizziness, headaches, weakness, and persistent vomiting, which were promptly relieved by increasing the amount of salt for 2 to 3 meals. The advocates of the salt-free diets claim that about 2 gm. of salt daily is sufficient for the average adult to cover the demand for body tissues and body fluids, and that these 2 gm. we get in a mixed diet from nature. However, I do not agree on this point, and personally I am absolutely against any diet, which "eliminates" salt entirely. An excellent scientific explanation on this subject was given by Bunge (4). This author states:

> Animals which feed exclusively on meat do not need salt. The acids formed in the metabolism in these animals are neutralized by bases formed by the breaking down of proteins. Potassium salts being present in vegetables cause an excess of potassium in the blood. In order to eliminate this, a large amount of sodium chloride is necessary. Therefore, all herbivorous animals need salt, and the same is true in man, who is omnivorous.

Since our diet asks for large quantities of raw vegetables and fruits, we must admit that we should "add" some salt to the diet, in order to eliminate the excess of potassium in the blood, and also to prevent a deficiency of sodium chloride. According to our clinical observations on

a great number of patients for four years, we may safely say that the addition of 2 gm. of salt to the diet daily is generally sufficient to protect the patient against either a deficiency or an excess of these minerals, and their consequences.

WATER METABOLISM

A very important point in this diet regimen is, the "reduction of the daily fluid intake of the patients."

Long before we had any knowledge of the existence of bacteria, the old surgeons knew that infiltration, inflammation, exudation, and pus-formation could be favorably influenced by a "drying-up" process of the body, and they used this method of treatment successfully by reducing the daily fluid intake of their patients. While the old surgeons applied this mode of treatment empirically, it was Dr. E. Puley (5) who proved scientifically, that, "normal tissue functions are controlled by their water content." Dr. Puley proved also that "sodium with its combinations, like sodium chloride, sodium bicarbonate, sodium phosphate, etc., all have the effect of attracting water, and causing 'exquisite swelling' (*Quellung*) of the cells," meaning retention and overflowing of the individual cells with fluid, or "hydration" of the body; while calcium, potassium, and magnesium, have the opposite effect, of exquisite "dehydration" (*Ent-Quellung*), meaning "emptying and clearing the cells from water." In his clinical observations, Dr. Puley was able to demonstrate that "chronic inflammations and pus-formations, as also infiltrations, exudations, and dyskeratoses,—all these phenomena, are strongly influenced by the water retention in the cells." Many clinicians have confirmed these findings.

In our diet regimen, we obtain the favorable effects of dehydration of the body, by restricting both the sodium with all its combinations and all liquids, and by the administration of calcium, potassium, and magnesium.

METHOD OF THE TREATMENT

General Rules

In order to be sure of securing a balanced metabolism, we must do the following:

1: Supply the patients with foods which are easily digested, assimilated, and absorbed.

2: Do not overfeed the patients; about 3,000 calories daily are enough.
3: Avoid, by all means, indigestion; because, during the time the state of indigestion lasts, and until a perfect recovery is established, the patient is not able to assimilate and absorb sufficient of the food-materials which are necessary for balancing the metabolism. The inevitable consequences which must follow are "deficiencies" of various important elements of the metabolism. These deficiencies, as we have seen above, may "increase the virulence" of the bacteria, and induce disastrous consequences in the patient.

Foods to be absolutely excluded

All smoked, spiced, and salty meats and fish.
Pork and veal of any kind and form.
Cream of Wheat; farina; and oatmeal. (Because, they are "powerful decalcifying" agents (Weston) (6)).
Vinegar; mustard; pepper; pickles of any kind.
White bread; cakes; pies; pastries; puddings; candies.
Dried peas; beans; lentils.

Permitted foods

Milk; cream (sweet and sour).
Rye and whole-wheat bread; noodles; macaroni.
Meats: beef; lamb; mutton; chicken; liver; kidneys.
Fish: all kinds. (fresh only).
Fats: Sweet butter; salt-poor-cheese; vegetable-oils; mayonnaise.
Fruits: all kinds (not canned).
Vegetables: all kinds (not canned).
Coffee and tea restricted; one cup of each daily.
Sugars: pure honey; marmalades; jellies; jams; fruit-juices; sugar: restricted.
Seasonings: lemons; ginger; parsley; vanilla; tomatoes.
Table-salt: 2 gm. daily.

Preparation of foods

No food should be fried.
Meats: broiled or stewed.
Fish: broiled or boiled.
Eggs: boiled or poached.
Potatoes: steamed; stewed; baked; boiled; and mashed.
Vegetables: steamed only.
Cereals: (whole grains only). Cold or cooked. If cooked, boil for 5–6 hours, and strictly strained.

Food materials for one patient per day:

	calories	*cost*
200 gm. (½ lb.) of meat	800	$0.15
100 gm. (¼ lb.) of sweet-butter	800	.10
1 pint of whole milk	200	.08
¼ of a pint heavy cream (40 per cent)	200	.06
300 gm. of raw vegetables	200	.10
300 gm. of raw fruits	300	.10
Bread and potatoes	300	.10
4 eggs (2 boiled; 2 yolks)	200	.10
Total: (approximately)	3,000	$0.79

Formula: P. 150; F. 150; C. 250 gm.; or, *high* in P. and F. and *low* in C.

Daily menus. Examples for one day:

B: Grape-fruit; corn flakes with cream; 2 eggs; bread; butter; coffee.
D: Steak; buttered spinach; baked potato; raw vegetables; milk.
S: Macaroni, cheese, butter; raw vegetables with mayonnaise; tea.

The daily diet routine, inclusive of medications

8 a.m.: Breakfast.
10 a.m.: 4 ounces of tomato-juice; 1 teaspoonful of calcium-gluconate; 5 drops of viosterol (on a small piece of bread); syrup hypophosphite co., dram 1.
12 noon: Dinner.
3 p.m.: 4 ounces of orange-juice; 1 yolk of an egg stirred in; and the same medications.
5.30 p.m.: Supper.
8 p.m.: 4 ounces of orange-juice; 1 yolk of an egg stirred in; and the same medications.

Festricted fluids:

Per day: 2 glasses of fruit and vegetable juices; 1 cup of coffee; 1 cup of tea; 2 glasses of milk. *No other fluids or water allowed.*

If a patient is inclined to hyperacidity, give potassium citrate in gr.-x doses; for constipation give milk of magnesia or magnesium sulphate, in dram-1 doses, several times daily.

Avoid all Sodium preparations.

CLINICAL RESULTS

Report of Cases

Case 1: (Bone-and-joint tuberculosis, involving spine, right elbow, and left knee). *S. L.:* White male, age 31. Onset of his condition in April, 1926. Patient suffered from severe pain in the spine, right elbow, and left knee, and was losing weight rapidly. Knee and elbow extremely swollen. He was treated in other hospitals without results, and was admitted to Cedar Crest Sanatorium in November, 1927. For the following 2 years at our Sanatorium, every effort in ordinary modern clinical and surgical treatment was made, but everything was in vain, the patient's condition growing worse. The swelling of left knee increased, there was fluctuation, which opened in 3 places and pus discharged freely. The pain in the spine grew so severe that he could not move his body in the least.

We put this patient on the new dietary treatment on September 1, 1929. After the second week, the pain in the spine and left knee improved, and the pus and swelling of knee decreased. At the 5th week, the discharge of pus stopped completely, and pain and swelling subsided.

At this time some difficulties in the Sanatorium's kitchen forced us to stop this treatment for a while. After the patient was back on the routine Sanatorium diet for about one week, the pus in the knee reappeared, and pain and swelling set in again; and after 3 weeks, the old hopeless condition came back again in every particular as it was described above before beginning this treatment. After 3 weeks of discontinuation, we started the new treatment again. After a few days, improvement set in; and after 5 weeks all pain subsided, discharge of pus from the knee stopped completely, granulations appeared, and the healing process was distinctly visible.

Results: After 8 months on this treatment, the patient was able to walk freely without any pain. Knee, spine, and elbow have healed completely, and he was able to leave the Sanatorium perfectly cured.

Observation of the same patient for a further 3 years discloses that he is doing his regular work, and is perfectly well.

Case 2: (Bone-and-joint tuberculosis, involving the left hip). *F. K.:* White male, age 21. Onset of his condition in November, 1928, with pain in the left hip-joint, aggravated by walking. Two fistulae formed which have been draining since that time. He was treated in other hospitals before without any results, and was admitted to Cedar Crest Sanatorium in July, 1930.

The routine Sanatorium treatment for the first 4 months did not bring any improvement. When this patient was put on the new treatment, improvement set in immediately. After 2 months, this treatment was replaced by the

routine Sanatorium diet, and the patient's condition was continually aggravated. For the following 16 months on the routine Sanatorium treatment, the patient grew worse. When he was put back on the new treatment again, the sudden favorable change was, in fact, amazing. After only 10 days, the draining of the 2 fistulae stopped completely; and after 3 weeks, the sinuses were perfectly healed.

Results: After 6 months, patient was able to walk without any support, and without limping, which he was not able to do for 4 years previously. We put him on very strenuous exercise, like walking up to 2 hours daily, and he grew stronger and felt better. What is more, the motion of the hip-joint is perfectly free in every direction. Now, he is able to ride a bicycle, and execute any motion with his hip-joint. He was able to leave our Sanatorium in less than one year on this new treatment, perfectly cured, whereas, he was considered "hopeless" before.

Case 3: (Bone-and-joint tuberculosis, involving right arm, left forearm, and right ankle joint). *F. D.:* White male, age 24. Present condition dates back 18 years ago, when he was 6 years old. Onset with pain, swelling, and redness of right arm (humerus). The arm was opened several times. General condition remained poor since. He was treated during childhood and adolescence in different sanatoria, but his condition remained the same. He was admitted to Cedar Crest Sanatorium in August, 1927. After 6 months at our Sanatorium, patient showed a new swelling on left forearm. Right arm kept on draining from 2 fistulae. One year later, a pectoral abscess was formed on right side, which was draining. In April, 1929, patient underwent a radical operation on right arm. This arm healed, but the general condition remained poor. About 9 months later, patient showed a new tuberculous process on right ankle joint. There was extensive swelling, redness, and tenderness, where it opened itself on 2 places, from which pus was discharging freely. At that time, he had lost 25 pounds since admission to Cedar Crest; his sedimentation rate was 48 per cent in 2 hours; and he was a strict bed patient.

Now, we started the new dietary treatment in February, 1930. There was a favorable change noted immediately. Local and general improvement was marked, and gradually increased.

Results: At the end of 7 months the patient had gained back 20 pounds; all fistulae were perfectly healed; and the sedimentation-rate went down, from 48 to 1 per cent in 2 hours.

He is working full-time at our Sanatorium, and I was able to observe him closely, for a further 3 years, and as he himself states: "he is getting stronger, he has gained an additional 15 pounds; and he is feeling better than at any time in his life."

Case 4: (Arthritis of lumbosacral spine; tuberculous.) *G. K.:* White male, age 57. Was admitted to Cedar Crest Sanatorium in April, 1932. Onset dates back about 38 years ago, after an injury, which he suffered while working in a coal-mine. A rock fell on his spine, when he was in a stooped position. After that, he was confined to bed for several weeks, unable to use his legs, and had severe pain in the back. He recovered so far that he could get out of bed, but he suffered pain in his spine, more or less severe, all these years. Several months before his admission to our Sanatorium, the pain in the back grew so severe that he had to give up his work. Chief complaints on admission were severe pain in the lumbosacral spine, day and night; even more severe at night, when lying in bed. Patient could not get any sleep, and, on account of this, he was failing rapidly. For the following 9 months at our Sanatorium, the routine treatment did not show any results; on the contrary, the patient's condition grew worse. He was losing weight; pain in the spine increased; the sedimentation-rate, which was 33 per cent in 2 hours on admission, went up to 55 per cent in 2 hours.

Now, we put this patient on the new treatment in January, 1933. According to his own story, he states: "Since the day he has started this new treatment, every day he has felt less and less pain; until, after 2 weeks, he did not feel any pain at all."

Results: After 4 months: He is free from all pain; is sleeping and eating well; has gained 20 pounds; and his sedimentation-rate has gone down from 55 per cent in 2 hours, to 16 per cent in 2 hours.

DISCUSSION

All cases reported demonstrate that patients, who did not respond to any treatment for many years previously, showed immediate curative effects after the beginning of this new treatment. Moreover, cases 1 and 2 demonstrate that, as soon as the patients started with this treatment, improvement set in; but that, shortly after we stopped the same treatment, an aggravation took place, only to improve immediately after we took up this treatment again. These facts can only be explained if we assume that the theory of our treatment is correct. Case 3 shows that the opinion of the modern surgeons is correct in that we cannot "cure" tuberculosis of the bones by a "local" radical operation, because "tuberculosis of the bones is a systemic disease with local manifestations;" and, therefore, new tuberculous processes are likely to appear at any other place. Case 4 is very interesting, because this case demonstrates that a tuberculous process, which did not respond to any treatment for 38 years, showed a curative effect in 2 weeks, with this new treatment.

SUN AND THIS TREATMENT

I have no intention to discuss here the therapeutic value of sun-treatment, in bone tuberculosis, but I only wish to state my clinical observations.

I did not expose my patients to the sun at all. I relied more upon the "pure" Vitamine-D (Viosterol), which we can give to the patients in a certain known dose, regularly, all year around, in order to secure an activation and an assimilation of the calcium.

REST AND THIS TREATMENT

"Rest" is very important in bone tuberculosis, "not" as a therapeutic measure, but for purely "mechanical" reasons. We can easily understand that soft, diseased and decalcified bones cannot be put upon too great strain and pressure without doing harm, and in this way delaying or preventing the process of healing. For this reason, I have my patients on "strict bed rest," until I am certain that recalcification and hardening of the bones have taken place.

SUMMARY

1. A method of treatment of tuberculosis is described and discussed.

2. In this article a report is made of bone-and-joint tuberculosis, and the clinical results as demonstrated by 4 cases.

3. The basis of this treatment is: "The correction of deficiencies of the metabolism and internal secretions of the patients."

4. Correction of deficiencies of the metabolism has the effect of "decreasing the virulence of the bacteria."

5. The addition of 2 gm. of sodium-chloride to the diet daily is generally sufficient to protect the patients against both, either a deficiency or an excess of these minerals and their consequences.

6. Chronic inflammations, and pus-formation, as also, infiltrations, and exudations, are strongly influenced by the water retention in the cells; we obtain the favorable effects of "dehydration" of the body, by restricting both, the sodium with all its combinations and all liquids; and by the administration of calcium, potassium, and magnesium.

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THE RELATIONS BETWEEN EXTRAPULMONARY AND PULMONARY TUBERCULOSIS[1,2]

DAVID REISNER

In the light of our present knowledge, there is no doubt that the various manifestations of tuberculous infection cannot be considered as separate entities. There is, on the contrary, a distinct tendency to look upon its manifold phases from a common point of view, and to comprehend their respective positions within the total course of the disease. Investigation of the factors governing the general course of the process and of the interrelation of its various appearances has been the object of numerous researches of the past few decades. The clear definition of the nature and of the importance of the primary focus, and the subsequent fundamental researches of Ranke (1) concerning the "cyclic course" of the tuberculous infection, furnished a particular stimulus for further investigations along these lines.

The relations between extrapulmonary and pulmonary tuberculosis offer a particularly pertinent problem in this connection. The behavior of the lungs in the presence of extrapulmonary lesions seems especially interesting in view of the fact that the lung is by far the most frequently involved organ in tuberculosis, both with respect to the primary lesion and later manifestations. Thus, it is only natural that this question should have been of interest to both clinicians and pathologists. One of the earliest observations in this direction is that of Koenig (2) in 1884, who failed to find any evidence of pulmonary lesion in a series of cases with skeletal tuberculosis. Marfan (3) has observed that patients, who during their childhood had suffered from tuberculous lymphadenopathies, were peculiarly resistant against later pulmonary involvement. The extreme rarity of active and progressive pulmonary lesions in tuberculosis of the skin, and especially in lupus vulgaris, has long been known. The significance of such observations becomes particularly impressive in view of more recent statements from sources of great experience, such as Aschoff (4) and Roessle (5), that there exists a distinct antagonism be-

[1] From the Sea View Hospital and the Department of Tuberculosis of the Metropolitan Hospital, New York City, Dr. George G. Ornstein, Director.

[2] Received for publication October 23, 1933.

tween the so-called surgical forms of tuberculosis and pulmonary lesions. Consequently, one is led to believe that there is a great deal more involved in this question than merely a matter of chance; that there are evidently inherent connections which govern the relations between these two groups of tuberculous manifestations.

The purpose of this study, therefore, is a detailed analysis of the pulmonary findings in extrapulmonary forms of tuberculosis, based on a series of cases sufficiently large to justify conclusions which might be reached. The main questions to be discussed here, are as follows: First, is there sufficient evidence of an antagonism between extrapulmonary and pulmonary lesions, and to what extent does it exist? Second, do the pulmonary changes observed in extrapulmonary tuberculosis present certain characteristic morphological and clinical features whereby they could be distinguished from the common forms of pulmonary tuberculosis, and in what proportion are they found in this association? Third, do such types of pulmonary lesions represent a particular pathogenetic entity?

It is evident that such a task involves to a great extent the question of finer qualitative differentiation of the various forms of pulmonary tuberculosis where the aid of careful roentgen-ray studies of the lungs is of prime importance. This is especially true in a material of the type dealt with here, in which, as will be seen later, one is frequently confronted with cases presenting little, if any, clinical symptoms referable to the pulmonary condition.

DEFINITION AND NATURE OF THE MATERIAL

In actual practice, the opportunities for a systematic study of the pulmonary findings in extrapulmonary tuberculosis, based on a material which would furnish a fair cross-section of the existing objective conditions, are rather limited. Up to the present, there still prevails the division into so-called surgical forms of tuberculosis and pulmonary lesions. The extrapulmonary lesions are distributed to a great extent through the various surgical services in general hospitals, while in the majority of the tuberculosis institutions they are found mostly in association with pulmonary lesions. The cases compiled for this series present the material from two large tuberculosis institutions, one of which serves all forms of tuberculosis, the other one predominantly pulmonary lesions. It seemed that a combination of this material would afford a closer approach to actual conditions.

Concerning the definition of extrapulmonary lesions, it must be emphasized that only cases presenting distinct organic manifestations have been included in this series; in other words, cases in which the character of the changes was of sufficient extent to give rise to a definitely manifest disease, both in the clinical and anatomical sense. It goes without saying that cases showing but a small number of abortive tubercles scattered through the organs, as frequently seen postmortem, cannot be regarded as chronic extrapulmonary tuberculosis in the above sense.

This series consists largely of two groups of extrapulmonary lesions, skeletal and genitourinary, with an additional small group of tuberculosis of the serous membranes, peritonitis or polyserositis (pleuritis, pericarditis and peritonitis). Although the lesions included in this material present wide dissimilarities as to the location, the extent, and severity of involvement, there are nevertheless important basic characteristics which they have in common. Of these the following are of particular significance in this connection: These lesions almost invariably represent secondary manifestations of the disease, having been preceded by a primary focus; they are as a rule metastatic in nature, and their haematogenous origin is practically certain, except in certain cases with involvement of the serous membranes, when other modes of infection may also play a rôle. Changes of the serous membranes due to direct extension of pulmonary or intestinal involvement were, of course, eliminated from this series, as they do not represent extrapulmonary lesions in the strict sense.

In table 1 the total material has been arranged according to the location and distribution of the extrapulmonary lesions.

TABLE 1

Distribution of extrapulmonary lesions

EXTRAPULMONARY LESIONS	NUMBER OF CASES	PER CENT
Skeletal lesions, solitary foci	111	46.2
Skeletal lesions, multiple foci	49	20.5
Genitourinary lesions	44	18.4
Combinations of genitourinary lesions with skeletal or other extrapulmonary involvement	22	9.1
Peritonitis and polyserositis	8	3.3
Combinations of peritonitis or polyserositis with other extrapulmonary involvement	6	2.5
Total	240	100.0

The total series consists of 240 cases, of which 160 (66.7 per cent), or two-thirds of the total, presented skeletal lesions,[3] 66 cases (27.5 per cent) genitourinary involvement, and 14 cases (5.8 per cent) had peritonitis or polyserositis. Nearly one-third of the skeletal lesions (49 cases) showed multiple foci; one-third of the genitourinary lesions (22 cases) presented combinations with other extrapulmonary involvement, chiefly with bone-and-joint lesions, and 8 cases showed multiple lesions of the serous membranes or an association of the latter with other extrapulmonary foci. Thus, 79 cases, or practically one-third of the total material, exhibited multiple metastatic manifestations. The remaining two-thirds, although comprising for the most part localized types, included nevertheless an appreciable number of cases with extensive and progressive involvement. It appears, therefore, that in this group are represented various clinical forms of extrapulmonary lesions, ranging from mild cases with localized solitary foci to the most severe types of a progressive generalized disease.

The material contains 169 (70.4 per cent) male and 71 (29.6 per cent) female patients. This relation corresponds quite closely with the general ratio of distribution of the sexes in the institutions from which this group has been collected. The genitourinary lesions involved predominantly male patients.

TABLE 2

Age-groups

AGE	NUMBER OF CASES	PER CENT
years		
14–16	4	1.7
17–20	30	12.5
21–30	84	35.0
31–40	55	22.9
41–50	45	18.7
51–60	17	7.1
61–70	5	2.1
Total.....	240	100.0

Table 2 demonstrates the distribution of the patients according to age, and reveals that the largest proportion, nearly one-half of the total (47.5 per cent), is found in the age-groups between 17 and 30 years, the third decade alone showing 35 per cent; then, with gradual declining

[3] The distribution of the skeletal lesions shows the spinal column as the most frequent location, with approximately 70 per cent of all skeletal lesions. Next in frequency is the hip-joint; then follows the knee, ankle and foot, elbow, shoulder, wrist and hand.

frequency all ages up to 70 years are represented. The average age for the total material was 33 years; it was decidedly lower, however, in the cases with skeletal lesions than in those with genitourinary involvement, which is quite in agreement with the well-known fact that the former, as a rule, have their onset in an earlier period of life than the latter. The youngest patient was 14 years of age, and there were only four individuals between 14 and 16. Children were not included, since this study was primarily concerned with conditions in adults. In children the conditions are decidedly different, especially with respect to the pulmonary findings, as will be seen further on.

The total duration of illness ranged between a period of several months and forty years. The average duration of illness for the total series amounted to six years. It is of interest to note that in the skeletal lesions the average duration of illness was twice as long as in the genitourinary lesions; seven years in the former, as against three and one-half in the latter. This fact is of considerable significance in view of the complications occurring in the genitourinary lesions which will be referred to in the course of a later discussion.

The length of time during which the patients were under observation varied between several months and twelve years; the average period of observation amounted to fifteen months.

ANALYSIS OF THE PULMONARY FINDINGS

In analyzing the pulmonary findings, the entire series will be considered at first as a whole, the differences concerning the various forms of extrapulmonary lesions to be discussed later. It should be stressed here that in grouping the pulmonary findings the decisive criterion was the presence or absence of actual intrapulmonary changes, of course, in so far as could be determined on the basis of detailed serial roentgen-ray studies.

Cases with negative pulmonary findings: In 116 cases (48.3 per cent), or nearly one-half of the total, no evidence of pulmonary changes could be found. Cases presenting signs of an old primary focus but no other changes were regarded as negative. Primary lesions were seen in 20 instances or in approximately one-sixth (17 per cent) of this group. Although the number of the primary foci appears relatively small, nevertheless caution must be exercised in evaluating this finding. It should be borne in mind that the mere fact that a primary focus is not demonstrated in the roentgenogram by no means precludes the possibility of its presence.

It is well known that even at autopsy table one is not infrequently confronted with considerable difficulties in searching for it. The obstacles will obviously be more pronounced for the radiographic demonstration during life, since the changes may be concealed by other intrathoracic structures, such as the heart, mediastinal organs, and diaphragm, or they may be superimposed upon the bony portions of the thorax. Although the possibility of a primary alimentary infection in some cases with extrapulmonary lesions cannot be disregarded, it is certainly not a frequent occurrence, especially in this country. In careful pathological investigations, Schuermann (6), Pagel and Henke (7) and Pagel (8) were able to demonstrate the presence of the pulmonary primary complex in the vast majority of their material, which comprised various extrapulmonary lesions and chronic generalized forms.

A considerable proportion of the patients with negative pulmonary findings presented evidence of other intrathoracic involvement, such as pleural exudates, in some cases as a part of extensive changes involving the serous membranes (polyserositis), or pleural thickening with adhesions. Marked enlargement of the tracheobronchial lymph nodes was found in a number of cases showing signs of a generalized tuberculous process. In several cases with clinical symptoms pointing to mediastinal pressure, these were found to be due either to lymphatic involvement or to a large paravertebral abscess secondary to caries of the spinal column.

There remain 124 cases (51.7 per cent), slightly more than one-half of the total, which showed definite evidence of pulmonary changes. The attempt has been made to group the pulmonary lesions chiefly according to the morphological findings. There is, however, as will be seen later, in most instances a corresponding clinical picture which characterizes the respective groups. It goes without saying that, as in every classification, it is often difficult to draw distinct lines of division. This is particularly true in pulmonary tuberculosis, in which one is confronted with a large variety of forms and phases, with many border-line types, and gradual transitions from one form into the other. However, there was a sufficient number of conspicuous common features to justify the division into the following groups:

1: Minimal or abortive lesions: Findings of this character were seen in 21 cases, which represent 17.0 per cent of the total cases with positive pulmonary findings. In most instances the changes were limited to the

FIG. 1

FIG. 2

FIG. 1. Scattered calcified nodules in both upper lung fields. Extrapulmonary lesion: tuberculosis of elbow and knee-joint.

FIG. 2. Discrete nodular foci in both apices. Extrapulmonary lesion: tuberculosis of kidney.

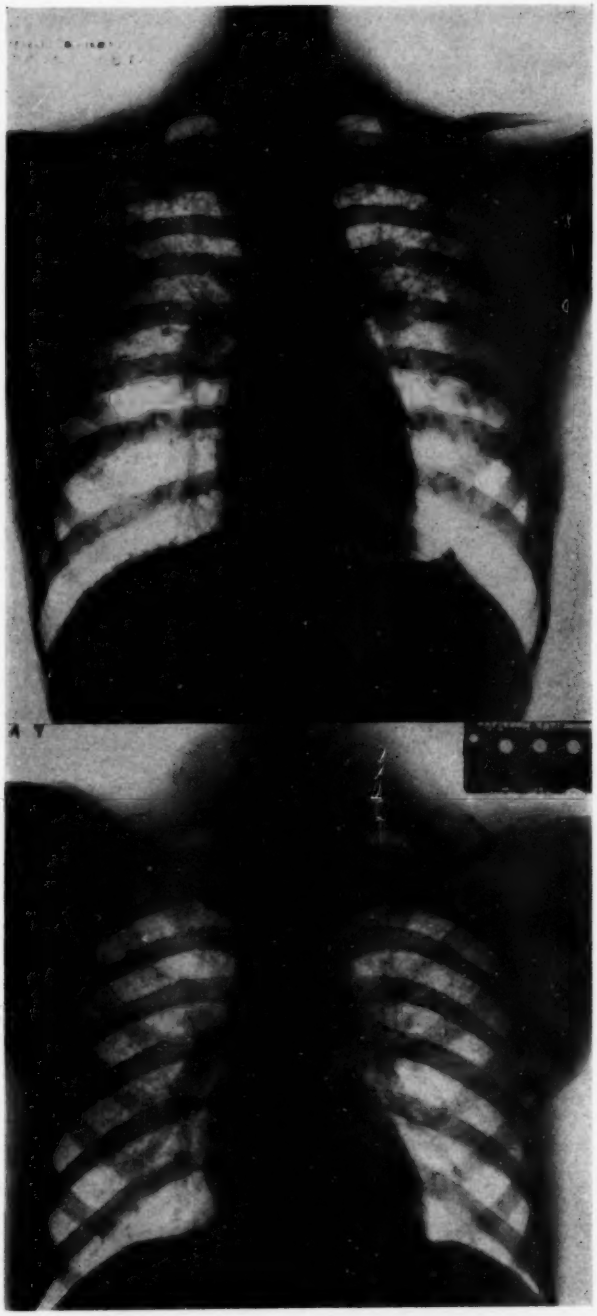

FIG. 3

FIG. 4

FIG. 3. Bilateral symmetrical discrete nodular dissemination involving the upper lung-fields. Extrapulmonary lesion; tuberculosis of knee-joint.

FIG. 4. Bilateral symmetrical chronic miliary dissemination involving the upper two-thirds of the lung-fields. Extrapulmonary lesion; tuberculous caries of lumbar spine.

apical areas, and frequently presented sparsely disseminated calcified nodules with a bilateral symmetrical distribution. Occasionally these foci could be seen extending further into the midfields or even down to the bases. In other cases there were scant discrete foci without calcification, also limited to the apices, with thickening of the apical pleura, corresponding to the fibrotic and indurative changes in the subpleural portions of the apices frequently noted as an incidental finding at the autopsy table (figures 1 and 2).

Clinically, these cases were asymptomatic; in several patients there was a suggestion of very mild symptoms in the past history. The sputum was persistently negative for tubercle bacilli in the entire group.

Pathogenetically, these changes are evidently of postprimary occurrence. Their haematogenous nature has been particularly stressed by Simon (9) and Huebschmann (10). The fact that these foci are predominantly situated in the apices, their usual bilateral symmetrical distribution, the fact that they can frequently be traced back to early childhood, and especially their relative frequency in association with extrapulmonary tuberculosis, speak in favor of a haematogenous origin. The particular disposition of the apices and upper pulmonic fields is probably a factor responsible for the typical location of the changes in these areas. These scattered foci in the lungs present an analogy with similar abortive disseminations of miliary tubercles not infrequently seen in the peripheral organs in cases of progressive pulmonary tuberculosis. In some cases in which a larger solitary calcified apical focus is found, this may be interpreted either as a healed reinfection focus of Aschoff-Puhl, or as one of the rare primary infections of the apex.

Although these changes are as a rule postprimary in origin, clinically they appear to be of no greater significance than an old primary focus, since they almost invariably represent a healed obsolete phase. It seems very unlikely that foci of this character could become the starting point of an active and progressive pulmonary phthisis.

2: Chronic disseminated lesions: This group includes cases showing decidedly more pronounced changes than the former. Although these lesions present considerable variations regarding the extent of the process, the differences are largely of quantitative nature. The qualitative morphological features remain quite conspicuous throughout the entire group, which includes 30 cases, or nearly one-fourth (24.2 per cent) of the total positive pulmonary findings.

Clinically, nearly all of these cases were of the latent type. Both the lack of subjective symptoms and the scarcity of physical findings frequently presented a striking contrast in comparison with the widespread objective changes as revealed by the roentgen-ray examination. Of the 30 cases of this group clinical symptoms referable to the pulmonary changes were completely absent in about one-half; the other half had very slight symptoms, chiefly of the type seen in emphysema and chronic bronchitis, and frequently concerned individuals of advanced age. The sputum was persistently negative for tubercle bacilli in 28 cases, only two patients occasionally had a few bacilli (Gaffky I or II).

The objective changes, as demonstrated by the roentgen-ray studies, presented various degrees in the extent of the lesion, ranging from involvement of a relatively small area to a diffuse spread through the entire pulmonic fields. However, the characteristic features, the disseminated distribution, and the discrete character of the foci, were quite constant. The dissemination is nearly always bilateral, with symmetrical involvement of both lungs to an equal level. There is a definite apicocaudate distribution, the foci gradually decreasing in number and in size from apex to base, with a distinct predominance in the upper fields. As to the nature of the foci, it is precisely in these types that a qualitative analysis on the basis of roentgen-ray studies is permissible, since their individual characters appear clearly preserved, and deductions regarding the underlying anatomical changes may be more readily drawn than in other forms of tuberculous involvement. The discrete nodular form with its transitions from the miliary tubercle to the more conglomerate foci of the acinonodose type (Aschoff-Nicol), the predominantly productive form, is a prominent feature in all these cases.

Several characteristic examples may illustrate the types commonly found in this group. A frequently observed form is a bilateral symmetrical dissemination involving the apices and subapical areas with a distribution of fine linear strands, evidently due to interstitial fibrosis; apical pleural thickening is almost invariably present. Another typical appearance is a bilateral dissemination extending to about the midlevel of the pulmonic fields, while the dependent portions are either free from changes or they may show sparsely scattered nodules. In still other cases the involvement appears to spread diffusely from the apices to the bases, the upper fields showing usually the more pronounced changes. An almost constant finding is increased translucence as a result of emphysema in the basal fields, but also frequently seen in the upper

portions within the involved area. Localized emphysema, as observed particularly in the infraclavicular portions, may resemble an area of rarefaction and may be erroneously interpreted as cavitation (figures 3, 4, 5, and 6).

It appears thus that this group presents various phases of discrete chronic disseminations showing features similar to the typical picture of acute miliary tuberculosis. They differ from the latter chiefly with respect to the quantity of the changes, the spread being more or less limited, in contradistinction to the massive seeding found in the typical acute cases. Occasionally, however, there can be seen cases with a diffuse chronic miliary dissemination, which, as far as the pulmonary changes are concerned, may be quite identical with those of the classical acute forms.

The chronic disseminated pulmonary lesions of the type described in this group have been of particular interest to the French School. Bard (11) has studied their clinical and pathological features, and incorporated these forms in his classification as *granulie discrete*, *sclerose dense* and *sclerose diffuse*. In the more recent French literature these lesions are often termed *granulies froides*, the chronic forms of miliary dissemination (Burnand and Saye (12), Rist, Rolland, Jacob and Hautefeuille (13), Bezançon and Delarue (14)). They conform to the lesions designated by Neumann (15) as *miliaris discreta*, *tuberculosis fibrosa densa*, and *fibrosa diffusa*. Neumann has contributed a detailed analysis of these forms describing their definite clinical entities and emphasizing their frequent occurrence in association with extrapulmonary tuberculosis. In the recently proposed clinical classification of pulmonary tuberculosis of Ornstein, Ulmar and Dittler (16), which has been adopted in our institutions, these types are included in the chronic proliferative forms.

A few words should be said here regarding the occurrence of healing in the disseminated types of pulmonary tuberculosis. Roentgenographic evidence of healing could actually be observed in some cases of this group, either complete disappearance of the foci or definite diminution in size and occasionally transformation into discrete calcific nodules. The discrepancy between these roentgenographic findings and the fact that absorption of true tuberculous granulation tissue is rather difficult to conceive of, is only an apparent one. The process which evidently takes place in these cases is not disappearance of the changes in the anatomical sense, but a considerable decrease in the size of the foci as a result of absorption of the perifocal inflammatory zone with subsequent connec-

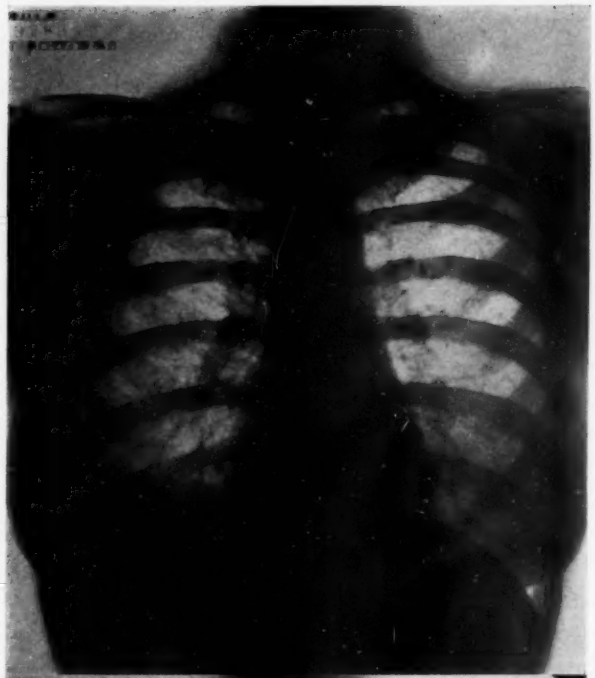

FIG. 5

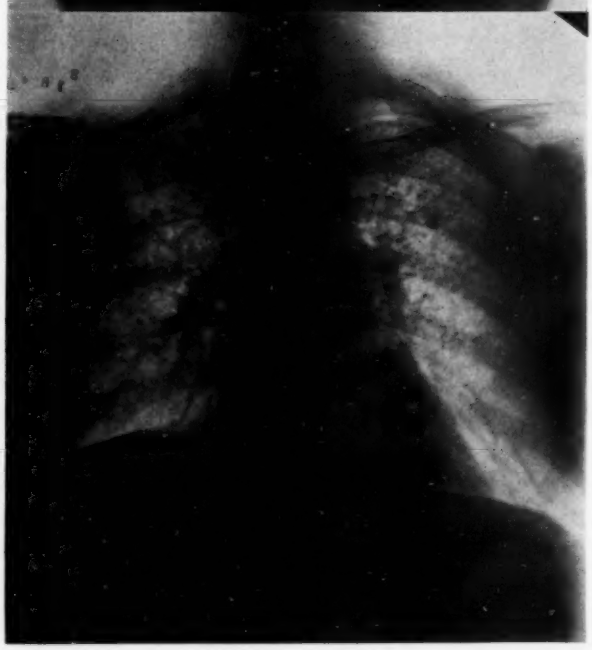

FIG. 6

FIG. 5. Bilateral diffuse chronic miliary dissemination. Extrapulmonary lesion: multiple skeletal involvement.

FIG. 6. Bilateral diffuse nodular dissemination of the acinonodose type. Extrapulmonary lesion: tuberculosis of elbow and genital organs.

tive tissue-formation and shrinkage. These secondary changes in conjunction with the resulting emphysema may account for the fact that such minute foci escape the detection on the roentgenogram.

The literature contains a number of reports concerning the healing of miliary tuberculosis, both from the pathological and clinical standpoint, such as those by Korteweg (17), Korteweg and Loeffler (18), Assmann (19) (20), Lorey (21), Kern and Johan (22), and others. As further anatomical evidence of healed miliary disseminations in the lungs, Schuermann (6) regards the finding of *lymphangitis reticularis*, which appears as a fine net-work of interstitial fibrosis. Occasionally this may be visualized roentgenographically in the form of fine linear strands. Such fibrotic changes, if sufficiently pronounced, will necessarily result in a loss of elasticity of the lung, which in turn leads to the formation of emphysema. It is quite evident, therefore, that the emphysema will often be the outstanding clinical manifestation in lesions of this type, as particularly emphasized by Neumann (15). It should be pointed out in this connection that some cases of emphysema of indeterminate origin in juvenile individuals may find their explanation in pulmonary lesions of a similar nature.

3: Chronic disseminated lesions with ulceration and cavitation: This group comprises 21 cases, or 17.0 per cent, of the total positive cases. In contrast to the preceding group, these cases presented definite pulmonary symptoms and positive sputum findings. It should be mentioned, however, that in a considerable proportion of these patients the history indicated an exceedingly chronic duration of the pulmonary lesion and that in some instances observation extending over several years showed little, if any, evidence of progression. More than one-half of these cases were individuals above forty years of age. These facts point to a markedly chronic and relatively benign course.

The morphological findings were fairly characteristic and presented a great similarity with those of the preceding group, showing a bilateral symmetrical nodular dissemination of various extent, with a continuous apicocaudate distribution. The distinguishing feature, however, was the presence of changes indicating ulceration and cavitation, in accordance with the clinical symptomatology and the positive sputum. The cavities found in these cases are as a rule small and multiple, usually of a symmetrical location in both lungs, often scattered, but showing no distinct predilection or relation to the topography of the lobes. Another

noteworthy feature is the almost constant absence of larger areas of pneumonic infiltration, which suggests that there is little tendency to gross bronchial aspiration into distant areas. It is quite remarkable that the discrete nodular dissemination remains preserved even in advanced cases of this type, in which the process of breaking-down may be marked in the upper fields, while the dependent portions retain the original character (figures 7 and 8). The roentgenographic demonstration of the cavities is frequently difficult because of the small size, the lack of a distinctly outlined wall, and the presence of diffuse changes. Localized emphysema within the involved portions offers an additional obstacle in the exact identification of the cavities.

The general character of the pulmonary changes in the preceding and in the present group seems to indicate their genetic similarity and their origin from an essentially identical type. However, in the former the original character of the lesion appears clearly preserved, while the latter shows superimposed changes with breaking-down and cavitation, features representing a further advanced phase of development which tends to blur the original picture. A careful follow-up of some cases of this group over a longer period of time, in which the evolution of the lesion could be studied, revealed the discrete productive nodular dissemination as the preëxisting finding, the ulceration and cavitation being a rather late manifestation, and not the source of the dissemination. This shows a distinct contrast with the usual sequence of events in most cases of exudative and caseous forms of pulmonary phthisis, where the cavity is an early occurrence and constitutes the source of the further spread of the lesion. It can be said that in the latter types the destruction and cavitation are essential and almost invariable features of the lesion, whereas in the group dealt with here they seem to be more in the nature of a secondary and accidental complication.

The pathological changes which take place here are evidently the result of breaking in of the interstitial foci into the bronchioles and larger bronchial ramifications with intracanalicular progression and subsequent ulceration. The type of pulmonary lesions described in this group corresponds to the form designated by Neumann (15) as *tuberculosis ulcerofibrosa*, which term indicates the development of a progressive and ulcerative lesion on the basis of a chronic disseminated productive form. The factors responsible for a transition of a hitherto quiescent and latent form into an active, exudative, and caseous lesion are probably closely related to the general conditions of immunity, and to the allergic state

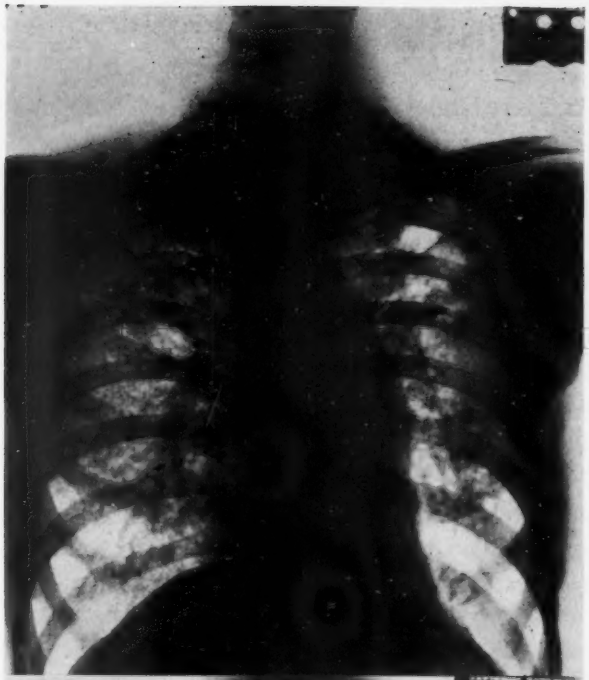

FIG. 7

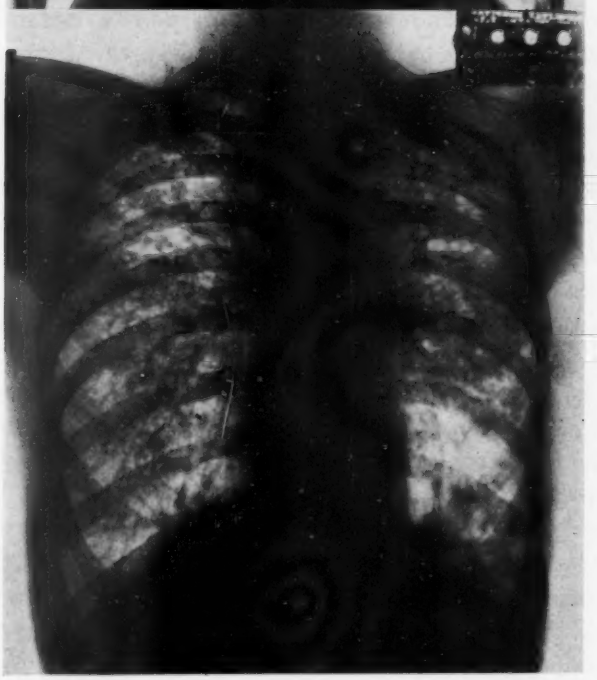

FIG. 8

FIG. 7. Bilateral symmetrical nodular dissemination, conglomeration and multiple small cavitations in the upper fields. Extrapulmonary lesion: tuberculous epididymitis.

FIG. 8. Bilateral symmetrical nodular dissemination, conglomeration and multiple small cavitations in the upper fields, more on the left. Extrapulmonary lesion: tuberculosis of epididymis and ankle.

of tissue reaction. The question whether these secondary changes are due solely to endogenous exacerbation, and to what extent they may be precipitated by added exogenous superinfections, cannot be determined with any degree of certainty. It must also be pointed out that the genetic identity of these lesions may often be difficult to establish, especially when the case is seen in an advanced stage and the continuity of evolution cannot be traced. Such cases may represent gradual transitions into the common forms of caseocavernous phthisis.

4: Acute disseminations: This group comprises 10 cases, or 8.0 per cent, of all cases with positive pulmonary findings. In these patients the miliary tuberculosis presented a terminal acute haematogenous dissemination complicating chronic extrapulmonary metastatic lesions. Six cases had genitourinary involvement, and 4 cases presented a picture of a chronic generalization with multiple skeletal lesions. All cases of this group died and postmortem examinations could be performed. Several patients developed the acute miliary dissemination following operative procedures for genitourinary or skeletal lesions. The significance of this fact, as well as the general relationship between the acute and chronic generalizations will be discussed later.

The remainder of the series, 42 cases (33.8 per cent), or one-third of all cases with positive pulmonary findings, exhibited morphological changes which did not conform to the types described in the preceding groups. Thus, the lesions found in these cases did not deviate in any definite manner from the usual and common forms of pulmonary tuberculosis. Clinically, too, these cases presented quite a different behavior; while in the former groups there was found a prevalence of the asymptomatic, latent and quiescent types, there was seen here a definite predominance of the active and progressive course. However, since the objective findings and the clinical course were not of a uniform character, a subdivision into three groups seemed necessary.

5: Caseopneumonic (fibrocaseous) forms: This group of 25 cases presented the usual picture observed in this type of pulmonary involvement. There was a predominance of more or less extensive pneumonic infiltrations, invariable progression to breaking down and cavitation, and a further spread into more or less distant areas as a result of gross bronchial aspiration. These changes appear diametrically opposed to those described in the former groups. The symptoms and clinical course were

quite in accordance with the objective findings and the sputum was nearly always positive. The character of the changes and the clinical picture of these lesions correspond with the caseopneumonic form of the previously mentioned classification of Ornstein and his collaborators (16).

It should be pointed out, however, that in some instances of this group the impression was gained that the changes represented far-advanced and late phases of the disseminated type, with superimposed ulceration and cavitation (as described under group 3), in which the secondary features have become predominant to such a degree as to obliterate the original form. It is also worth mentioning that in a number of cases there were found cavities of a typical appearance, mostly multiple, either thin-walled or without any radiographically demonstrable shell, often surrounded by normal pulmonary structure. Their appearance corresponds to the "punched-out" cavities (*lochgestanzte Kavernen*), described by Schuermann (6) (23), Pagel and Henke (7), and Pagel (8) as a characteristic finding in chronic generalizations. This form of cavitation is evidently a hyperergic manifestation and may develop as a result of acute infiltration, caseation and ulceration, which is followed by a rapid elimination of the necrotic material. This mechanism would explain the rapid development of these cavities and the absence of a spread resulting from bronchial aspiration. In this series, however, the number of cases showing such changes was rather limited; and it is questionable, therefore, whether they can be considered as a characteristic pulmonary finding in extrapulmonary lesions.

6: Cirrhotic lesions: Findings of this type were seen in 12 cases. The outstanding changes were a pronounced tendency to fibrosis and induration, resulting in shrinkage and contraction of the lung. Clinically, these lesions show an exceedingly chronic duration and their course is for the most part stationary. In a number of instances a follow-up extending over a period of several years showed very little tendency to progression. One-half of the cases had persistently negative sputum; the others showed a few bacilli occasionally. The clinical course and the negative sputum frequently presented a sharp contrast with the extensive radiographic findings, a behavior often encountered in the so-called senile forms of phthisis.

7: Benign exudative lesions: These could be observed in 5 cases, and the patients, upon subsequent follow-up, presented complete or almost complete clearing of the lesion, concomitant with improvement in their

subjective condition. In several instances the sputum, which at first contained occasional tubercle bacilli, later became persistently negative. The findings in these cases correspond with the benign and evanescent types of exudative tuberculous infiltrations described by Wessler and Jaches (24), Fleischner (25), Assmann (26), Redeker (27), and others, and more recently by Ornstein and collaborators (28).

COMMENT

A recapitulation of the pulmonary findings reveals that in 48.3 per cent or in nearly one-half of the total material there was no evidence of post-primary pulmonary involvement; the remaining 51.7 per cent presented changes of a diverse nature which were divided into a number of groups. Table 3, in which the cases with positive pulmonary findings are presented as a separate group, shows the relative proportions of the various types of lesions.

TABLE 3

Distribution of the positive pulmonary findings

	NUMBER OF CASES	PER CENT
1. Minimal and abortive lesions	21	17.0
2. Chronic disseminated lesions	30	24.2
3. Chronic disseminations with ulceration and cavitation	21	17.0
4. Acute disseminations	10	8.0
5. Caseopneumonic (fibrocaseous) lesions	25	20.1
6. Cirrhotic lesions	12	9.7
7. Benign exudative lesions	5	4.0
Total	124	100.0

The result of this analysis reveals a *strikingly large proportion of the discrete nodular disseminated forms of various quantitative extent*, ranging from a small number of foci of the abortive type with frequent indications of healing and calcification (21 cases of group 1), through various degrees of dissemination of the chronic miliary and acinonodose type (30 cases of group 2), to the typical acute miliary tuberculosis (10 cases of group 4)—a total of 61 cases. There are in addition 21 cases of group 3, disseminated nodular forms with superimposed ulceration and cavitation, which probably originate from similar basic types, as indicated by the foregoing description. Thus, 82 cases, or two-thirds (66.2 per cent), of all cases with positive findings, presented distinctive morphological features of the pulmonary involvement.

Their outstanding and typical characteristics are as follows: the disseminated distribution; the distinctness and small size of the foci and the preservation of their original character; the continuous apicocaudate spread, with predominance of the changes in the apical and upper fields, and the gradual decrease in size and number of the foci toward the dependent portions; finally, the symmetrical involvement of both lungs. It is readily seen that the chronic lesions of this type have a number of features in common with the typical acute forms of miliary tuberculosis. It should be pointed out that the above-mentioned unequal distribution of the changes, which favor the upper fields, is also frequently encountered in the acute forms of miliary disseminations. A number of observers have called attention to this fact: among others, Ribbert (29), Kaufmann (30), Beitzke (31), Huebschmann (10), Pagel and Henke (7). *The pronounced morphological and topographical similarities between the chronic disseminations and the acute forms of miliary tuberculosis, and particularly the frequent association of the former with extrapulmonary lesions, are points in favor of their haematogenous origin.*

Clinically these lesions are characterized by a predominance of the latent forms; in the majority of cases, symptoms referable to the pulmonary involvement are either completely absent or very slight. This disproportion between the paucity of symptoms and physical signs on the one hand, and the objective changes as demonstrated radiographically on the other, is quite striking. To be sure, in a number of instances there is a tendency to progression and ulceration, which may obscure the original character of the lesion, although the clinical course frequently remains stationary and relatively benign.

The above findings conform to the clinical and roentgenological descriptions of similar forms by Grau (32), May (33), Assmann (19), Diehl (34), Lydtin (35), Neumann (15), and others. The characteristic features of the pulmonary changes found in this material are also borne out by the results of the more recent pathological investigations of Huebschmann (10), Schuermann (6), Pagel and Henke (7), and Pagel (8) (36). The careful studies of these authors revealed, among other typical features of the pulmonary changes in extrapulmonary lesions, the following findings: a considerable proportion of more or less diffuse and uniform chronic nodular disseminations of a bilateral symmetrical character, atypical forms of miliary tuberculosis; pronounced healing tendencies, as indicated by frequent transformation of the granulation tissue into nodules composed of hyaline connective tissue and interstitial fibrosis of the type of *lymphangitis reticularis*. The preservation of the original small size of

the individual foci is probably due to very slight exudative tissue reactions in these lesions, which may account for the fact that there is little or no tendency to progression. In this connection it is of interest to quote the results of a pathological investigation by Aidelsburger (37) from Aschoff's Institute, who found a striking predominance of the productive forms of pulmonary lesions in cases with extrapulmonary manifestations; while the ratio of distribution of productive and exudative types was fairly equal, 1 to 1, in pulmonary tuberculosis without extrapulmonary lesions; it amounted to 9 to 1 in favor of the productive forms in the cases in which extrapulmonary lesions were present. Other pulmonary findings regarded by Pagel as characteristic features in chronic generalizations and in extrapulmonary tuberculosis, such as the "punched-out" cavities and evanescent exudative infiltrations, were present only in a limited number of instances, and thus could not be considered as characteristic manifestations on the basis of the results obtained in this material. The relative frequency of preceding or associated pleuritis in cases with disseminated pulmonary lesions should be mentioned here. The superficial, subpleural and cortical situation of the foci in these lesions, as pointed out by Pagel (8), may well be the cause of the comparatively frequent pleural involvement.

In contrast to the groups considered hitherto, the pulmonary changes of the last three groups (5, 6 & 7) exhibited no definitely distinctive features; they represent types which do not differ from the common forms of pulmonary tuberculosis. These groups include 42 cases, or 17.5 per cent of the total material, and comprise about one-third (33.8 per cent) of the cases with positive pulmonary findings.

The prominent features of these lesions are pneumonic infiltrations with caseation, ulceration and cavitation, and distinct relations of the involved portions to the topography of the bronchial ramifications and of the lobar divisions. The initial manifestation of the lesion is as a rule unilateral, and provides the source of the further extension of the process which is brought about by focal or massive bronchial aspirations, frequently into more or less distant areas. This spread also shows a definite relation to the anatomical distribution of the bronchial tree. The evolution of these lesions frequently proceeds in a wave-like course, with phases of exacerbations and remissions, which applies both to the clinical course and the corresponding pathological changes. Thus, the mode of progression is by no means a continuous apicocaudate distribution, as typically seen in the disseminated forms; on the contrary, the discontinuous character

of the spread is the more common occurrence, and it is quite remarkable that the true apical field not infrequently remains uninvolved even in cases in which the changes are far advanced. This development can be particularly well demonstrated in cases in which a careful serial follow-up from the early beginnings of the lesion is feasible.

The outstanding features of the pulmonary changes, as they appear in typical examples of the reinfection type of pulmonary tuberculosis, were briefly summarized here in order to illustrate the decided difference as compared with the previously discussed forms. These changes correspond with the chronic tertiary form of Ranke (1), in which the spread by contiguity and the intracanalicular bronchial extension dominate the development of the pathological process in the lungs. The problem of their early phases and of their evolution have been the subject of numerous investigations in recent years. The clinical and roentgenological observations of Wessler and Jaches (24), Assmann (26) (38) (39), Redeker (27) (40) (41), Redeker and Walter (42), and Neumann (15), have brought forward interesting and valuable information in this particular domain.

It must be stressed, however, that in this series not all cases with noncharacteristic pulmonary lesions were of a uniform nature. Of the 42 cases only 25 (group 5), 10.4 per cent of the total, or 20.1 per cent of the positive cases, showed changes of a more or less pronounced progressive caseocavernous tuberculosis; 12 cases (group 6) were of the chronic cirrhotic type with a fairly stationary clinical course; 5 cases (group 7) were of the benign exudative type with indications of absorption and clearing of the lesion.

A brief résumé of the results of this analysis from the clinical standpoint reveals the following: Symptom-free were 116 cases of the negative group, the entire group 1 with minimal and abortive changes comprising 21 cases, and one-half, or 15 cases, of group 2 with disseminated lesions, making a total of 152 cases (63.3 per cent), or nearly two-thirds of the total material. Very slight and insignificant clinical symptoms were present in 26 cases (10.8 per cent), and 52 cases (21.7 per cent) had symptoms ranging from a moderate to a severe degree with definite signs of activity. The remaining 10 cases were patients who developed a terminal acute miliary tuberculosis. Thus, about one-fifth of the total had to be considered as clinically active pulmonary lesions. It should be pointed out, however, that a considerable proportion of these cases ran a definitely stationary course and presented little or no evidence of pro-

gression. This was particularly the case in the group with chronic disseminated lesions which were complicated by ulceration and cavitation (group 3).

The result of the sputum examination was quite in accordance with the clinical symptomatology. In 42 cases (17.5 per cent) the sputum was more or less persistently positive for tubercle bacilli. In several instances presenting definite clinical and roentgenological indications of active lesions, no record of sputum examinations was available. There were in addition 11 cases in which the sputum was practically always negative, but occasionally a few bacilli (Gaffky I or II) were present, or in whom the initially positive sputum became persistently negative on subsequent follow-up, as in some of the benign exudative lesions.

DISCUSSION

On entering into the general discussion of the relationship between extrapulmonary and pulmonary tuberculosis, it is essential first to clarify a point which has a direct and important bearing upon the problem of the so-called antagonism between these two groups of tuberculous lesions. This question concerns the place which the extrapulmonary lesions occupy within the general course of the tuberculous infection, and more specifically, to what extent they occur as more or less localized manifestations of the disease. In other words, does the concept of the chronic isolated organic phthisis, the tertiary form of Ranke (1), which evidently holds true for the majority of the chronic pulmonary lesions, apply with equal justification to extrapulmonary tuberculosis?

Do the extrapulmonary lesions represent isolated organic or generalized systemic forms of involvement? A survey of the material from this point of view reveals the following: 161 cases (67.1 per cent), or two-thirds of the total, had largely solitary extrapulmonary manifestations, or, in a small proportion, extensive involvement limited to a single anatomical system, as in a number of cases with marked genitourinary changes. In 79 cases (32.9 per cent), or in one-third of the total, there was evidence of multiple clinically manifest lesions, as presented in detail in table 1.

If the pulmonary findings of these two groups are now taken into consideration, not counting the minimal and abortive changes, the following figures result: In the first group with chiefly solitary extrapulmonary lesions, 87 cases, or 36.3 per cent of the total, were practically free

from pulmonary involvement, in other words they had no other clinically manifest changes; the remaining 74 cases of this group (30.8 per cent) presented, in addition to the extrapulmonary involvement, definite pulmonary changes of more than abortive character. The second group, the cases with multiple extrapulmonary manifestations, contained 29 instances (12.1 per cent), in which there was evidence of pulmonary involvement in addition to the multiple extrapulmonary lesions. Thus, only slightly more than one-third (36.3 per cent) of the cases of this series could be considered as showing the character of chronic isolated extrapulmonary lesions, while nearly twice as many cases (63.7 per cent) presented multiple organic manifestations, either multiple extrapulmonary metastases or solitary extrapulmonary foci with pulmonary involvement.

Loewenstein (43) (44) and Huebschmann (10) prefer to speak of tuberculosis of systems of organs (*Organsystem-Tuberkulose*) rather than of single organs. This is based on the observation that the infection frequently involves anatomically identical or similar structures in various regions of the body, and gives rise to the appearance of multiple foci, either simultaneously or successively. Examples of such types are multiple lesions involving the skeletal system, the genitourinary tract, the serous membranes, multiple involvement of the lymph nodes, and others. It is of interest that metastatic manifestations in other systemic structures may be conspicuously absent in these cases. Such types may occupy an intermediary position between the isolated forms and the chronic generalized forms; their general characteristics, however, are decidedly more of the latter type.

The predominance of lesions with multiple manifestations appears particularly striking when the cases which died during the course of the observation are considered as a separate group. A review of these cases is especially valuable, as it permits one to draw more definite conclusions regarding the ultimate fate in this type of lesions. Out of 91 cases which could be followed to the time of death only 14 (15.4 per cent) presented the character of chronic isolated extrapulmonary lesions; 15 cases (16.4 per cent) had more or less widespread systemic manifestation, such as multiple skeletal metastases, multiple genitourinary lesions, or extensive involvement of the serous membranes; the remaining 62 cases (68.2 per cent) presented combinations of involvement of two or more anatomical systems, either with or without pulmonary changes.

It appears, therefore, that the predominant majority of extrapul-

monary lesions represents chronic generalized forms of various degree and severity, whereas the so-called isolated tertiary character is evident only in a minority of instances. The outstanding feature of the former is the predominantly haematogenous extension of the process which gives rise to multiple metastatic foci in various organs. These manifestations may appear simultaneously, but more often they occur at successive intervals, and the entire disease-process may extend over a period varying from a few months to many years.

These types conform to a great extent to those described by Schuermann (6) (23) as a chronic protracted progressive systemic infection (*chronisch protrahierte progressive Durchseuchung*). It seems that these cases fail to attain the stabilization of the resistance and the degree of relative immunity which is apparently necessary to localize the disease and to counteract the inherent tendencies toward further generalization of the infection. This again shows the distinct contrast as compared with the vast majority of chronic pulmonary lesions. Clinically, these forms frequently show a labile course with unexpected and unpredictable development of new phases and symptom-complexes as a result of a spread of the infection through various organs.

The rôle of the pulmonary involvement in extrapulmonary tuberculosis: In view of the character of the extrapulmonary lesions, with their pronounced tendencies toward generalization of the process and spread by way of the circulation, it is not surprising to find in these cases a large percentage of pulmonary involvement. Apart from this factor, however, which is of a general nature, there are additional causes which seem to have a decided bearing upon the particular frequency of the coexisting pulmonary changes in these lesions. Owing to the important rôle which the lung plays in primary infection and because of the anatomical peculiarities of the pulmonary circulation, this organ appears most intimately connected with the sources of origin of extrapulmonary lesions, as well as with their further evolution. To be sure, the exact pathogenesis of extrapulmonary lesions in general and of chronic generalized forms in particular, especially the question as to the actual source from which they are derived, is not entirely clear as yet. Of the most likely possibilities which enter into consideration the following should be mentioned here: the primary complex which may remain virulent and active and give rise to repeated invasions of bacilli into the circulation, usually indirectly by way of the lymph nodes and lymph-vessels;

the "endogenous lymphoglandular reinfection" of Ghon and Pototschnig (45) and Ghon and Kudlich (46); a postprimary pulmonary focus, or an extrapulmonary focus discharging showers of bacilli into the circulation; finally, a chronic tuberculobacillaemia of indeterminate origin (Loewenstein (43) (47) (48) and Liebermeister (49) (50) (51)). Whatever the actual cause may be, it is evident that in all of the above mentioned modes of infection the lung represents a sort of an interpolated filter for the bacilli, the effect of which will be frequent pulmonary changes resulting from haematogenous disseminations.

It seems, therefore, that the above-considered factors are sufficient causes to account for the frequency with which pulmonary involvement is found in extrapulmonary lesions. Whether the specific sensitivity of the lung to tuberculous infections plays an additional rôle as a predisposing factor, is merely a matter of conjecture, although it should be mentioned that this point has been stressed by a number of authors. Of course, the possibility of additional exogenous superinfections must not be entirely disregarded.

Having recognized the extrapulmonary lesions as showing to a great extent the character of chronic, more or less pronounced, generalized forms of tuberculosis, the emphasis of the question as to the participation of the lungs should be placed not so much on their absolute frequency as on the qualitative type and the degree of the changes. With respect to the absolute frequency of the pulmonary changes, no definite antagonism could be demonstrated between extrapulmonary and pulmonary lesions on the basis of the material of this series, since more than one-half of the total presented evidence of positive pulmonary findings. If, however, the qualitative character and the degree of the pulmonary changes, as related in detail in the analysis of the pulmonary findings, are taken as a criterion, there appears a distinct antagonistic relation to the common every-day forms of pulmonary phthisis and especially to those of the active and progressive types.

All these considerations point to the conclusion that *the pulmonary involvement found in association with extrapulmonary forms of tuberculosis represents in the majority of instances a part of a chronic generalized process*, the changes having originated by way of an endogenous spread, chiefly through the haematogenous route; only in a minority of cases are the pulmonary lesions of a type corresponding with the common forms of the reinfection phthisis.

Skeletal and genitourinary lesions in their respective relations to the pulmonary changes: Thus far, the entire material has been dealt with as a whole. It appears advisable to inquire into the relation of the pulmonary findings to the individual forms of extrapulmonary lesions, and to see whether this might not throw some additional light on the problem.

In table 4 the pulmonary findings are arranged separately for the two main groups of extrapulmonary lesions, the skeletal and genitourinary involvement.

TABLE 4

PULMONARY FINDINGS	SKELETAL LESIONS		GENITOURINARY LESIONS	
	cases		*cases*	
Negative	84	(52.5%)	22	(33.4%)
1. Minimal and abortive lesions	12	(7.5%)	9	(13.7%)
2. Chronic disseminated lesions	19	(11.9%)	10	(15.2%)
3. Chronic disseminations with ulceration and cavitation	9	(5.6%)	12	(18.2%)
4. Acute disseminations	4	(2.5%)	6	(9.0%)
5. Caseopneumonic (fibrocaseous) lesions	19	(11.9%)	4	(6.0%)
6. Cirrhotic lesions	9	(5.6%)	3	(4.5%)
7. Benign exudative lesions	4	(2.5%)		
Total	160	(100.0%)	66	(100.0%)

A comparison between these two groups, which constitute 94.2 per cent of the total material, reveals a decisive difference in their relations to the pulmonary changes. While the skeletal lesions show in 52.5 per cent entirely negative pulmonary findings, there are only 33.4 per cent negative cases in the genitourinary lesions. Moreover, there is a decidedly larger proportion of the active and progressive pulmonary lesions in the latter, than in the former group. These data are entirely in agreement with the results obtained by Huebschmann (10) on the basis of autopsy material, who found that coexisting pulmonary involvement is far more frequent in genitourinary lesions than in any other type of extrapulmonary lesion. Also combinations with other extrapulmonary foci are more frequently observed in genitourinary than in skeletal tuberculosis.

The above comparison indicates that the skeletal lesions have a more pronounced tendency to preserve their extrapulmonary character with exclusion of pulmonary changes than the cases with genitourinary involvement. The typical examples of "chronic isolated" forms of

extrapulmonary tuberculosis, comparable in every respect with corresponding types of pulmonary lesions, are best seen among the skeletal lesions. The involvement of the spinal column represents a classical illustration of this type. The solitary nature of the extrapulmonary lesion is more frequently encountered in these cases than in any other form of extrapulmonary tuberculosis. In the cases with Pott's disease of the spine of this series, the lungs were found entirely negative in 66.8 per cent, and 3.6 per cent showed only very slight changes of the abortive character, which makes a total of 70.6 per cent of essentially negative cases; only 14 per cent presented pulmonary changes of the active and progressive type. These data conform fully with the well-known clinical observations regarding the infrequent occurrence and benign character of the pulmonary changes in vertebral caries.

The difference between the skeletal and genitourinary lesions in their relations to the pulmonary changes suggests some interesting points in connection with this subject. Skeletal tuberculosis is, as generally known, principally a disease of childhood and period of growth, while lesions of the genitourinary tract usually occur later in life, predominantly at the age of puberty and in young adults. It is quite possible, therefore, that a localized skeletal lesion acquired during early childhood exerts an immunizing influence and increases the general resistance against later reinfections (Aschoff (4), Rollier (52)). A typical example pointing in this direction is the above-mentioned vertebral tuberculosis, which is largely a disease of childhood. Such a mechanism is obviously less likely to prevail in the case of genitourinary lesions. Because of their onset in a later period of life the chances for preceding infections, both exogenous and endogenous, appear considerably greater. A further important factor which probably has a bearing upon the more frequent association of tuberculosis of the urinary tract with pulmonary involvement is the excretory function of the kidneys, as particularly pointed out by Huebschmann (10); the involvement of the urinary organs is not infrequently a secondary manifestation due to progressive and extensive pulmonary lesions.

Further analysis of the material from the standpoint of whether there are definite relations between the extent and severity of the extrapulmonary lesions and the type and degree of the pulmonary involvement, did not reveal any conclusive points. There was no sufficient evidence to indicate either a parallel course, such as extensive extrapulmonary lesions with correspondingly severe and progressive pulmonary involvement,

nor was there a definite antagonistic relation noted as far as the extent and progression of the lesions were concerned. An analysis of the previously mentioned group of 79 cases with multiple extrapulmonary manifestations, representing largely extensive and severe forms, did not reveal any appreciable difference in their relations to the pulmonary findings as compared with the total material. It seems, therefore, that the extrapulmonary and pulmonary lesions pursue to a great extent their independent course, and that the fate of the one does not necessarily influence the other.

It should be pointed out, however, that in a number of instances of extensive extrapulmonary lesions which at first presented negative or very slight pulmonary changes, there could be seen simultaneously with the aggravation of the general condition a corresponding terminal flare-up and rapid progression of the pulmonary lesion. Such occurrences are evidently due to a break-down of the immunity forces resulting in a terminal anergic phase with consequent defenseless progression of the lesion.

Causes of death in extrapulmonary lesions: An inquiry into the eventual causes of death in extrapulmonary tuberculosis should be of value in connection with this subject. In the previously mentioned group of 91 cases which could be followed to the time of death, the following distribution was found: In 38 cases (41.7 per cent) death appeared to be due to extensive extrapulmonary lesions with multiple metastases in various organs, marked toxaemia, and general cachexia. Ten cases (11 per cent) died from acute miliary tuberculosis, and 9 cases (9.9 per cent) developed terminally clinical symptoms of meningeal involvement. Active and progressive pulmonary lesions of sufficient extent to be considered as a cause of death were present only in 11 cases (12.1 per cent), although the proportion of cases showing positive pulmonary findings amounted to more than one-half of the total. In 10 cases (11 per cent) death was due to intercurrent diseases, such as nontuberculous pneumonia, or to postoperative complications, and in 7 cases (7.7 per cent) to amyloidosis. In the remaining 6 cases (6.6 per cent) the cause of death could not be definitely established.

These data reveal two points which merit special attention. The first is the fact that terminal miliary tuberculosis and meningitis seem to provide a frequent cause of death in extrapulmonary lesions; they were present in more than one-fifth (20.9 per cent) of the cases of this group. The frequency of these complications in association with chronic extra-

pulmonary lesions is in distinct contrast to their comparatively rare occurrence in pulmonary lesions. Weigert (53), in 1879, was the first to call attention to the strikingly rare finding of acute generalized miliary tuberculosis in chronic pulmonary lesions, an observation corroborated in subsequent years by a number of other authors (Brasch, Benda, Schuerhoff, Silbergleit and others, quoted after Grethmann (54)), and more recently stressed by Huebschmann (10, 55). This antagonistic relation certainly does not apply to extrapulmonary lesions; on the contrary, the opposite seems to be the case here. This is indicated by the above findings as well as by a number of other observations pointing to the frequent occurrence of miliary tuberculosis and meningitis in extrapulmonary lesions in general, and more particularly in cases with genitourinary involvement. Simmonds (56) found that about one-third of the cases with tuberculosis of the genital organs die from these complications, whereas in pulmonary lesions they were present in only 5 per cent. Tuberculous meningitis was observed by Kaufmann (30) in 33 per cent of the lesions involving the genitourinary tract. Kuemmel (57) stressed the comparatively frequent occurrence of acute miliary disseminations as a postoperative complication in renal tuberculosis, which can be corroborated on the basis of this material. A similar observation was made by Koenig (2) in skeletal lesions. These facts are further important indications that the pronounced tendency to generalization constitutes a distinct characteristic of the extrapulmonary lesions.

The second significant point is the fact that only in a relatively small proportion of the cases could death be attributed to an extensive pulmonary lesion. It is noteworthy that almost identical results were obtained by Aidelsburger (37) on the basis of a large autopsy material. This author found that in a series of cases which presented a combination of both extrapulmonary and pulmonary tuberculosis, the latter was the cause of death in only 13 per cent, whereas in pulmonary lesions without extrapulmonary manifestations death was directly attributable to the pulmonary changes in 65 per cent, a ratio of 1 to 5. These data are quite in accordance with the frequently benign character of the pulmonary changes in extrapulmonary lesions, as related in preceding paragraphs. It is also of interest to mention that intestinal and laryngeal involvement is much more frequent in chronic isolated pulmonary lesions than in pulmonary changes which are associated with extrapulmonary manifestations (Pagel (8)). This is of considerable significance, since the involvement of the larynx and the intestines as a rule runs parallel with the extent and severity of the pulmonary lesions.

Review of literature: In consulting the literature on the subject of the relations between extrapulmonary and pulmonary tuberculosis, one finds numerous references to the strikingly rare occurrence of manifest and active pulmonary changes in tuberculosis of the eye, in various forms of tuberculous skin lesions, and in lymphatic involvement (Lewandowsky (58), Witkina and Maklakova (59), Marfan (3), Wallgren (60), and others). The chief interest, however, lies in a comparison of data which have been obtained from types of lesions corresponding to the material of this series. Loewenstein (43) (44), in reviewing the post-mortem examinations in 400 cases of skeletal and genitourinary tuberculosis, reported results almost identical with those obtained by the writer, the lungs having been found free from changes or showing insignificant apical scars in 60 per cent of the skeletal and in 40 per cent of the genitourinary lesions. Data compiled from clinical material were reported by Ostenfeldt (61), de Bloeme (62), Alwens and Flesch-Thebesius (63), Ragolsky (64), Ganowsky and Rosowa (65), Steindler (66), Bumpus and Thompson (67), Beck (68), and Peters (69). The proportion of manifest and active pulmonary lesions found by these authors varies mostly between 15 and 21 per cent, which is in fair agreement with the results obtained in this series. One finds that the predominance of the latent and benign types is persistently stressed; there is, however, little reference to the particular forms of the pulmonary lesions, their clinical or pathological significance.

A considerably lower proportion of coexisting active and progressive pulmonary lesions is observed in children. In skeletal lesions Schaffhausen (70) found such changes in 6 per cent; Kremer and Wiese (71) only in 3 per cent. A gradual increase in the frequency of the pulmonary changes concurrently with the transition from childhood to adolescence is noted from the data obtained by Johansson (72), who followed a considerable proportion of his cases with skeletal lesions over a period of many years. It should be added, however, that limited haematogenous disseminations of a more or less abortive character with signs of healing are by no means infrequent in children with extrapulmonary lesions. It is questionable whether the occurrence of alimentary infections and the alleged frequency of the bovine organism in some extrapulmonary lesions of the childhood age, such as skeletal, lymphatic or peritoneal involvement, have an important bearing upon the low incidence of pulmonary lesions in these cases; this especially in view of the widely divergent reports of various observers (Griffith (73) (74), Jones and Lovett (75),

Moellers (76), Kremer and Wiese (71)). The high figures of the bovine organism are probably due to particular conditions prevailing in certain localities (Scotland) and cannot be considered as having a general significance. The low incidence of pulmonary involvement in children with extrapulmonary lesions is, after all, only in line with the general conditions prevailing in childhood. The deciding factors probably are more limited opportunities for reinfection, and possibly also greater healing tendencies in mild haematogenous disseminations, as mentioned above.

Marked discrepancies with respect to both the absolute frequency and the particular types of the coexisting pulmonary changes may also be due in a great measure to a one-sided selection of the material. It is evident that reports originating from surgical divisions will inevitably show a lower incidence than those obtained from tuberculosis institutions. This is illustrated by the fact that the proportion of active and progressive pulmonary involvement was three times higher among the cases collected from The Tuberculosis Department of the Metropolitan Hospital than in those from the Sea View Hospital. This marked disproportion seems adequately explained by the different character of the institutions, the former being destined largely for pulmonary tuberculosis, while the latter includes both the so-called surgical and pulmonary lesions. It was thought that by combining the material of these two institutions it would be possible to obviate this important drawback.

Pulmonary tuberculosis as a whole in relation to extrapulmonary involvement: It is quite essential to consider the problem of the relationship between pulmonary and extrapulmonary lesions also from the opposite angle; namely, to what extent does the pulmonary tuberculosis at large show a tendency toward further spread of the process through the peripheral organs resulting in manifest extrapulmonary foci? In this connection the term extrapulmonary foci must be restricted, of course, to changes of metastatic nature which are due largely to a spread by way of the circulation. Hence, changes brought about by local extension of the pulmonary process, such as pleural or pericardial involvement, or a continuation of the lesion by way of preformed anatomical pathways, such as intestinal and laryngeal changes, cannot be regarded as extrapulmonary lesions in the strict sense.

It has long been a common experience of both pathologists and clinicians that, in comparison with the widespread distribution of pulmonary tuberculosis, manifest extrapulmonary lesions represent a strikingly

rare occurrence. To be sure, not infrequently there is found at post-mortem examination evidence of a limited past or terminal hematogenous dissemination, as shown by the presence of a small number of tubercles in the peripheral organs, such as in the kidneys, liver, spleen, and adrenals. These foci, however, are merely of an insignificant abortive character; they exhibit no tendency toward progression, and hence cannot be considered as manifest extrapulmonary lesions from the clinical and practical standpoint.

A review of the literature with particular reference to the types of extrapulmonary lesions presented in this series, reveals the following data: Johansson (72) cites the results of an investigation by an official Dutch committee which found 2.52 per cent skeletal and lymphatic involvement in a group of 1,510 cases of pulmonary tuberculosis. A similar figure, 2.7 per cent, was found by MacKinnon (77) in a series of 1,058 cases with skeletal lesions. Rosow and Japolsky (78), in an investigation of an autopsy material consisting of advanced forms of pulmonary lesions, found changes involving the skeletal system or the serous membranes in only 1.5 per cent. Genitourinary changes present a more frequent complication: Roshdestwensky (79) found them in 5.6 per cent, and Fishberg (80) in 10 per cent of the pulmonary lesions. This conforms with the previously mentioned findings regarding the more frequent association of pulmonary lesions with genitourinary involvement.

A review of the material of the Tuberculosis Department of the Metropolitan Hospital for the past two years reveals the following: Among 1,222 cases including *all* forms of pulmonary lesions there were 53 instances, or 4.3 per cent, with clinically manifest extrapulmonary involvement; 29 cases had skeletal lesions, 16 genitourinary changes, and 8 cases presented peritonitis or polyserositis. The proportion is decidedly different, however, when the active and progressive pulmonary lesions alone are considered. In 1,027 cases of this type there could be found 29 cases, or only 2.8 per cent, with definite evidence of extrapulmonary involvement.

It appears, therefore, that pulmonary tuberculosis at large, and especially the active and progressive types, presents a distinctly more pronounced antagonistic relation to the extrapulmonary lesions than *vice versa*. The conspicuous absence of metastatic manifestations in the course of pulmonary tuberculosis is all the more striking in view of the fact that there are undoubtedly ample possibilities for the bacilli to enter into the circulation, particularly in the ulcerative and destructive forms.

Indeed, there seems to be sufficient evidence to indicate that such invasions actually take place. It is well known that tubercle bacilli are not infrequently present in the blood-stream in cases of extensive pulmonary lesions, especially in the terminal phases (Loewenstein (47) (48), Liebermeister (49) (50); for complete literature see Loewenstein (81)). Nevertheless, extrapulmonary foci of sufficient extent to be considered as a manifest source of disease are comparatively rare. In the vast majority of cases there is found either no evidence of a haematogenous dissemination, or at the most only scattered foci of abortive character, as mentioned above. However, it is interesting to note that toward the terminal phases of an isolated progressive pulmonary phthisis one may occasionally observe the appearance of a clinically manifest extrapulmonary focus such as a solitary skeletal or genital lesion, especially in elderly individuals. It is quite possible that such changes are due to an exacerbation of a quiescent abortive focus as a result of the break-down of a formerly acquired relative state of immunity. This presents a parallel with the previously mentioned terminal progression of the pulmonary changes in some cases with extensive extrapulmonary lesions.

Thus it is quite evident that *the character of the chronic isolated organic forms is definitely more clearly preserved in the pulmonary than in the extrapulmonary lesions.* The latter represent only in a minority of instances chronic isolated lesions analogous to the pulmonary tuberculosis, whereas the majority of cases show a distinct tendency toward an endogenous propagation and generalization of the infection, which leads to multiple organic manifestations either with or without pulmonary involvement. It is also in keeping with the general nature of the extrapulmonary lesions that acute miliary disseminations and meningitis are found as a relatively frequent complication in these cases, as contrasted with their rare occurrence in pulmonary lesions.

It seems rather difficult to explain this totally different behavior of tuberculous infection solely on the basis of accidental invasions of bacilli into the circulation. Such fundamental differences cannot be accounted for unless the inherent factors governing the total course of the disease and especially the variable conditions of immunity and allergy are taken into consideration. These forces probably have a decided bearing upon the fact that in spite of frequent opportunities for a haematogenous spread, the disease remains more or less localized in the majority of individuals with pulmonary involvement, whereas the cases with extrapulmonary lesions exhibit pronounced tendencies toward generalization. If one were

to apply Ranke's (1) conception of the cyclic course in tuberculosis, it might be said that the predominant majority of the chronic pulmonary lesions represent the tertiary forms, where the isolated organic disease and a certain degree of relative general immunity are the outstanding features; the extrapulmonary lesions, on the other hand, seem to retain to a great extent the characteristics of a retarded secondary stage with a more or less protracted endogenous spread of the process.

Chronic isolated haematogenous forms of pulmonary tuberculosis and their differentiation: A further question to be discussed is whether the forms of chronic pulmonary tuberculosis described here as a frequent and characteristic finding in extrapulmonary lesions are also encountered without manifest extrapulmonary involvement. It must be stated that pulmonary lesions of an identical character are not infrequently observed in cases which present no evidence of extrapulmonary metastases. To be sure, these forms occur with particular frequency and present a most typical appearance in cases with coexisting extrapulmonary manifestations. However, there is no doubt that a chronic haematogenous dissemination may remain limited to the lungs and not give rise to clinically manifest foci elsewhere. It seems reasonable to assume that the conclusions regarding the origin and the pathogenesis of these forms of pulmonary involvement will apply with equal justification in the absence of manifest extrapulmonary foci, provided that the changes exhibit the characteristic morphological and clinical features, as described in detail in the preceding chapters. The acute miliary tuberculosis can be looked upon as an extreme event which expresses a particularly severe type of reaction. This may be due either to a massive invasion of bacilli into the blood-stream, or to a hyperergic state of sensitivity, or to a combination of both factors. It is obvious, however, that, given a limited invasion and a lowered state of reactivity, there may result more or less extensive chronic haematogenous disseminations of various degree and severity. In 1883, Weigert (82) had already stressed the distinction between acute and chronic haematogenous forms of tuberculosis, and suggested a differentiation of three types according to the extent of the changes and the severity of the course. The significant point is the fact that in all these occurrences the lung occupies a central position and will thus show the results of a chronic haematogenous spread to a more pronounced degree than any other organ. The importance of the haematogenous origin in chronic forms of pulmonary tuberculosis has been emphasized in the past

by a number of pathologists, especially by Ribbert (29) and more recently by Huebschmann (10). Ribbert could observe various degrees of chronic haematogenous disseminations in the lungs from the very limited forms to the typical acute miliary tuberculosis.

The chronic disseminated haematogenous lesions must be differentiated from somewhat similar tuberculous changes which are due to a bronchogenous spread. This may occur following severe haemoptysis, with resulting aspiration and spread by way of the bronchial tree. However, the preceding haemoptysis, the almost invariable presence of gross areas of infiltration and cavitation, as well as the different morphological character and mode of distribution, will as a rule provide a number of points for differentiation.[4] A further differential diagnostic possibility may be a diffuse bronchial spread due to a direct perforation of a caseated lymph node into a large bronchus. However, a discrete nodular spread is not likely to occur in such cases; usually this complication produces more or less massive pneumonic infiltrations; it involves predominantly children and the general clinical picture is as a rule quite severe.

Practical considerations: From the clinical and practical standpoint the following must be stressed: complete absence of pulmonary changes by no means excludes the possibility of the tuberculous aetiology of a questionable extrapulmonary lesion. This is indicated by the results obtained in this series of extrapulmonary lesions, in which nearly one-half of the total material failed to present any evidence of pulmonary involvement, aside from the old primary complex. On the other hand, it cannot be too strongly emphasized that in a number of instances with extrapulmonary manifestations of obscure aetiology the roentgen-ray examination of the chest may be of distinct diagnostic value, although both subjective symptoms and physical signs referable to the lungs are entirely absent. Because of the particular frequency of clinically latent forms of pulmonary involvement in extrapulmonary lesions, the roentgen-ray examination alone may be in a position to decide the diagnostic issue.

In addition, being aware of the particular relationship which exists between extrapulmonary lesions and the forms of pulmonary tuberculosis described here, it seems advisable to search routinely for other organic manifestations, if confronted with such types of pulmonary involvement. In doing so one may be able to detect extrapulmonary changes which otherwise are apt to escape clinical recognition.

[4] The effect of haemoptysis in pulmonary tuberculosis upon the spread of the lesion is being investigated, and will be the subject of a separate publication.

SUMMARY AND CONCLUSIONS

1. The relations between extrapulmonary and pulmonary tuberculosis were studied on the basis of a series of 240 cases with clinically manifest extrapulmonary lesions which included the most frequent forms of extrapulmonary involvement. The material consisted chiefly of skeletal and genitourinary lesions; a small group of tuberculosis of the serous membranes, peritonitis or polyserositis, was also included.

2. In nearly one-half (48.3 per cent) of the total the lungs were either entirely free from changes or at the most presented evidence of an obsolete primary focus. Slightly more than one-half of the material (51.7 per cent) showed evidence of postprimary pulmonary involvement.

3. The differential analysis of the pulmonary changes from a morphological standpoint, based on careful roentgen-ray studies, revealed that approximately two-thirds (66.2 per cent) of the cases with positive findings exhibited as the most prominent features discrete nodular productive disseminations with a bilateral symmetrical distribution. As to the quantitative extent of these forms, various degrees of involvement were found; abortive types with sparsely scattered foci, numerous transitional forms of chronic disseminations of the miliary and acinonodose type with a more or less diffuse spread, and typical acute miliary disseminations. In one-third (33.8 per cent) of the cases with positive pulmonary findings, or in 17.5 per cent of the total material, no definitely characteristic morphological features could be found; this group presented the common forms of chronic pulmonary phthisis.

4. The pronounced morphological and topographical similarities between the chronic disseminated forms and the acute miliary disseminations and particularly the frequent occurrence of the former in association with extrapulmonary tuberculosis, are decisive points in favor of their haematogenous origin.

5. The predominant majority of the chronic disseminated forms shows a distinct tendency to retain the typical morphological characteristics. In some cases, however, progressive changes with ulceration and cavitation may take place which tend to obliterate the original features.

6. The analysis of the material from the clinical standpoint revealed that only about one-fifth of the total (21.7 per cent) presented evidence of active pulmonary lesions. The disseminated forms are as a rule clinically benign and latent, unless secondary changes with progression occur; the contrast between the extent of the process as demonstrated by the

roentgen rays and the scarcity of clinical signs and symptoms is often very striking.

7. The extrapulmonary lesions represent in the majority of instances chronic generalized forms of tuberculosis showing a tendency toward endogenous propagation of the infection, which leads to multiple organic manifestations, either with or without pulmonary involvement. The character of the chronic isolated organic phthisis (Ranke) was apparent in only about one-third of the total series. The predominance of the generalized forms was even more conspicuous in the cases in which the ultimate fate of the disease, that is, the condition at the time of death could be studied.

8. The pulmonary changes in extrapulmonary tuberculosis represent in the majority of cases a part of a chronic progressive endogenous generalization. The frequency of pulmonary involvement in these lesions is enhanced by the peculiarities of the pulmonary circulation and the rôle of the lung as a filter for circulating bacilli.

9. From the standpoint of the mere frequency of the pulmonary changes, no definite antagonism could be noted as between extrapulmonary and pulmonary involvement. There is, however, a distinct antagonistic relation to the reinfection types of pulmonary tuberculosis, especially to the active and progressive forms.

10. The pulmonary tuberculosis at large presents a definitely more pronounced antagonistic relation to extrapulmonary involvement than *vice versa*; manifest extrapulmonary lesions are conspicuously rare in the common forms of pulmonary tuberculosis. The type of the chronic isolated phthisis is the general rule in pulmonary lesions, in contradistinction to the extrapulmonary forms.

11. Acute miliary tuberculosis and meningitis present a comparatively frequent cause of death in chronic extrapulmonary lesions, as contrasted with their rare occurrence in chronic pulmonary lesions. This is consistent with the predominantly generalized character of extrapulmonary tuberculosis.

12. Extensive and progressive pulmonary tuberculosis cannot be considered as a frequent cause of death in extrapulmonary lesions, if compared with the total proportion of coexisting pulmonary changes in these cases. This constitutes further evidence of the frequent benign and nonprogressive character of the pulmonary involvement in extrapulmonary tuberculosis.

13. The frequency of pulmonary involvement is considerably lower

in skeletal than in genitourinary lesions. The character of the chronic isolated extrapulmonary lesion is distinctly more manifest in the former than in the latter; it is most pronounced in the cases with tuberculous caries of the vertebrae.

14. Various degrees of chronic haematogenous disseminations may occur in the lungs without clinically manifest extrapulmonary involvement.

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THE MANAGEMENT OF ADHESIONS IN ARTIFICIAL PNEUMOTHORAX

A Clinical Analysis of 200 Consecutive Cases with a Description of Technique and New Instruments[1,2]

J. W. CUTLER

With the more widespread use of therapeutic pneumothorax in the treatment of pulmonary tuberculosis it would seem desirable to attempt to define the indications and contraindications for severing adhesions, to discuss methods of management, and to describe improved instruments and technique that have been useful. With these questions in mind I have reviewed the case histories and serial X-ray films of 200 consecutive patients in whom a pneumothorax could be established that have come under my observation for varying periods during the past four years. The material is gathered from the ambulatory pneumothorax clinic at The Henry Phipps Institute, from the Deborah Sanatorium, New Jersey, and from private practice.

TYPES AND INCIDENCE OF ADHESIONS

Adhesions of one sort or another were found in 173 of the 200 cases studied, or in more than 86 per cent. These figures do not indicate, of course, that adhesions are a surgical problem in that percentage of cases, but they suggest that by the time the patient presents himself for diagnosis and therapeutic pneumothorax is induced, adhesions are the rule and not the exception. In this series no cases are included in which collapse could not be established, or had to be abandoned shortly after institution.

A classification of adhesions is necessary to a proper understanding of their significance, since the difficulties to be overcome vary with the type of adhesion present. Any classification must of necessity be arbitrary, and some adhesions are extremely difficult to assign to any one group. The most logical is perhaps that based upon the anatomical appearance

[1] From the Henry Phipps Institute of the University of Pennsylvania, Philadelphia, Pennsylvania.

[2] Presented at a Clinical Session of the 30th annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, May 16, 1934.

of the adhesion, in line with the writings of Jacobaeus, Matson, and others who have given considerable attention to this subject.

Adhesions may be roughly divided into three general groups: *strings*, *bands*, and *apical caps*. In each group there may be several varieties.

Strings are the most common intrapleural adhesions. They were seen in the X-ray films of 117 cases of the 200 studied, or in 67 per cent of the 173 cases in which adhesions were found. In 78 cases they were the only type of adhesion seen. Although they may be found in any part of the pleural cavity, they usually extend from the apex of the lung to the apical pleura or laterally to the 1st and 2nd interspaces in the axillary region. As a rule they are multiple. The great majority of string adhesions can stretch readily and may reach a length of 10 cm. or more. They may vary in diameter from the fineness of a hair to the thickness of one's little finger. The latter are often referred to as *cord* adhesions, and are usually shorter than strings, and often of more mechanical importance.

Bands were found in 45 cases, or 26 per cent of those with adhesions. They are commonly associated with strings (27 cases) but they may occur alone (18 cases). They vary in width from 1 to 10 cm. They are usually fleshy. The majority have a short stump of 4 cm. or less, or none at all. With the latter type the lung is fastened directly to the chest-wall. Band adhesions not infrequently contain good-sized blood-vessels and lung tissue. Like string adhesions, they are found chiefly in the upper third of the chest running laterally to the axillary region or upward to the apical pleura.

There are several varieties of band adhesions, such as the fan-shaped, with a broad thoracic attachment and a narrow pulmonary attachment, and the funnel-shaped, with a broad pulmonary attachment and a narrow thoracic attachment. These two are often spoken of as the *tent type*. Dumb-bell or spool-shaped adhesions are a combination of the fan- and funnel-shaped varieties, with broad visceral and parietal attachment and a narrowing in the middle.

The third and in many instances the most troublesome type is the apical cap. This may completely envelop the apex of the lung and extend downward as far as the 5th posterior rib in the axillary space. It may overlie large stiff-walled cavities and not infrequently it forms part of the cavity wall. Apical-cap adhesions are fairly common. They were found in 50 cases, or 29 per cent of those with adhesions, and in 38 cases they were the only type of adhesion observed.

In 39 cases, 22 per cent, mixed types were found in the same chest.

The most common combinations were strings and bands, in 27 cases, followed by apical caps and strings or cords, in 12 cases.

It is worth mentioning that had thoracoscopy been feasible in every one of the 200 cases studied more adhesions would have been discovered than were recorded in the X-ray films, in which some were hidden behind other structures.

Adhesions having a thoracic attachment above the anterior 2nd rib are called *apical*; those having a parietal attachment below the 2nd rib are called *lateral*; and those attached to the diaphragm are called diaphragmatic adhesions, for example, apical strings, lateral bands, etc.

THE CLINICAL SIGNIFICANCE OF ADHESIONS

There is a wide difference of opinion among phthisiologists and thoracic surgeons as to the clinical necessity for severing adhesions. O'Brien (1), after studying the records of 250 patients in whom artificial pneumothorax had been established sufficiently long to judge end-results, found only 6 patients, 2.4 per cent, in whom the adhesions were of such a nature as to suggest that intrapleural pneumolysis should have been performed. Matson (2), in reviewing 268 cases subjected to artificial pneumothorax, found adhesions suitable for pneumolysis and preventing a satisfactory collapse in 31, or 11 per cent. Stivers (3) believes that in 80 per cent of patients given pneumothorax the lung is ineffectually collapsed owing to pleural adhesions, and that in many of these cases surgical intervention is advisable.

In considering the problem, one should first of all exclude those cases in which, although adhesions are present, there is no cavity to be collapsed and the sputum is negative. The mere presence of an adhesion, however easily it can be severed, is not in itself an indication for surgey. It may be accepted as an axiom that it is not necessary to have a perfect collapse of a diseased area in order to obtain an anatomical cure. Moreover many adhesions, if given enough time, will stretch and permit closure of apparently uncollapsable cavities. Other cavities will close if the pneumothorax is supplemented by operations on the phrenic nerve (Slavin (4)), or by scaleniotomy (Clyne (5), Fisher (6)), or by fixation of the mediastinum followed by frequent high-pressure pneumothorax refills. There is still, however, a group in which the cavity cannot be closed except by pneumolysis or else by the more drastic procedure of thoracoplasty.

In the series upon which this paper is based there were 36 cases in which

the cavities remained open because of adhesions after due allowance had been made for the element of time, fixation of the mediastinum, and the advisability of phrenic evulsion and scaleniotomy. These 36 cases are 18 per cent of the 200 cases in which pulmonary collapse was possible and advisable, and 20 per cent of the 173 in which adhesions were present. In other words every fifth case, approximately, of those subjected to pneumothorax therapy had adhesions of mechanical importance. This is not, however, a complete statement of the problem, for we can also

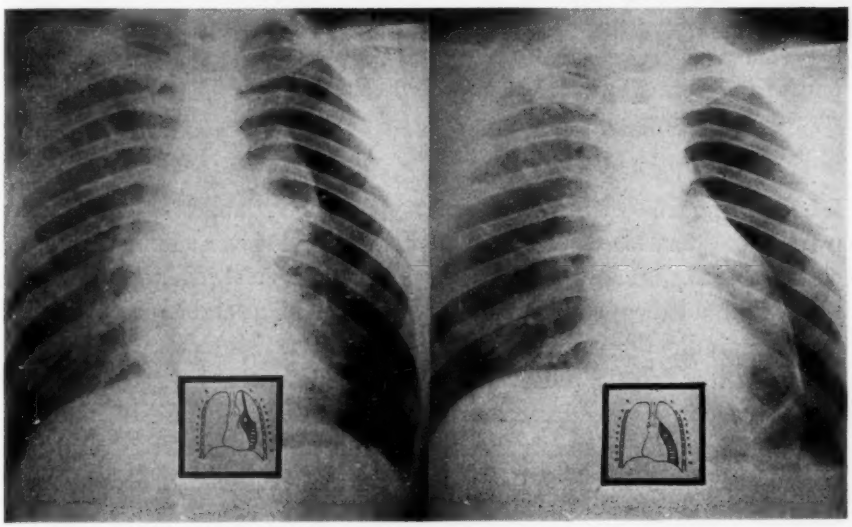

FIG. 1 FIG. 2

FIG. 1. Case 1, D. G. Single cord adhesion nine months after pneumothorax treatment was instituted. This adhesion probably would in time have stretched sufficiently to permit closure of the cavity, but the cavity meanwhile was increasing in size and the patient experienced serious haemoptysis.

FIG. 2. Case 1, D. G. Prompt closure of the cavity following pneumolysis. The operation was relatively simple. Such cases can be treated with less risk, and can be saved considerable expense and invalidism through early surgical intervention.

safely extend the usefulness of the operation through earlier and wider intervention to save time and expense both to the patient and to the community, in keeping with the best practices in tuberculosis therapy. The following instance is illustrative.

Case 1: D. G., white, male, 26 years of age, was first given pneumothorax treatment for advanced tuberculosis of the left upper lobe with cavity-forma-

tion and positive sputum on June 2, 1932. An apical cord adhesion was encountered, which prevented closure of the cavity. The adhesion, however, stretched continuously under the pressure of the induced pneumothorax and it was hoped that in time it would permit complete closure. By March, 1933, nine months after the induction of the pneumothorax, the adhesion had stretched to 9 cm. (figure 1). In the meantime, however, the cavity had increased in size and now measured 4 by 3.5 cm. The patient developed a series of severe haemoptyses and there was extension of the disease into the right or "good" lung. It was therefore not thought wise to postpone surgical intervention any longer, and on March 30, 1933, I severed the adhesion with the operating forceps-thoracoscope (7) without difficulty. There was a mild postoperative reaction for a few days; the cavity promptly closed (figure 2). The patient's general condition has improved considerably and there has been no recurrence of haemoptysis.

A critical analysis of this case in the light of its history shows that a *laissez-faire* management was in fact not without danger. The adhesion would doubtless have continued to stretch, and, given enough time, the cavity would probably have closed without surgical intervention. But meanwhile the disease was progressing in both lungs and haemoptysis had occurred, indicating the risk involved in delay. Moreover the ease and safety with which the adhesion was eventually severed suggests that the patient might readily have been saved months of invalidism and considerable expense if pneumolysis had been undertaken much earlier in the course of his illness. The value of prompt action can also be measured in terms of the economic and social value of an earlier return to health.

In reviewing my material from this point of view I feel that pneumolysis was desirable in at least 63 patients, or 36 per cent of the 173 presenting adhesions. Thus, in my opinion, every third case of those given pneumothorax (31 per cent of the 200 cases) had adhesions that should have been severed. I believe that this figure more closely approximates the frequency with which this operation is indicated in the average run of patients suitable for artificial pneumothorax, than the percentage of cases in which it was found essential for successful collapse (18 per cent).

Table 1 shows the incidence of the various types of adhesions observed in this study arranged in the order of their clinical importance. It is evident that the frequency and the clinical significance of adhesions will vary widely with the type of case placed under treatment, whether early or far advanced, acute or chronic. The wide discrepancies in the figures

given in the literature may be in part explained by differences in the material on which they are based. The most troublesome apical caps and bands are naturally found more frequently in far-advanced, chronic cases, and strings occur most often in earlier cases.

In the series reported here there were 78 cases in which string adhesions alone were found. Only in 6 of these, or 8 per cent, was pneumolysis essential. On the other hand, there were 38 cases in which apical caps alone were encountered, and pneumolysis was essential in 14, or 37 per cent. These figures express more exactly the indications for the operation with various types of adhesion than do figures based on consecutive series, with their wide variations in the type of case included. That

TABLE 1

The clinical significance of adhesions complicating 173 among 200 consecutive cases treated by artificial pneumothorax

TYPE OF ADHESION	CASES HAVING ADHESIONS		PNEUMOLYSIS NOT INDICATED		PNEUMOLYSIS NOT ESSENTIAL BUT DESIRABLE		PNEUMOLYSIS ESSENTIAL		
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	
Apical caps and strings	12	6.0	5	*42*	2	*16*	5	*42*	2.5
Apical caps (alone)	38	19.0	23	*60*	1	*3*	14	*37*	7.0
Strings or cords and bands	27	13.5	15	*56*	3	*11*	9	*33*	4.5
Bands (alone)	18	9.0	12	*67*	4	*22*	2	*11*	1.0
Strings or cords (alone)	78	39.0	55	*70*	17	*22*	6	*8*	3.0
	173	86.5	110	55	27	13.5	36	—	18

Note: The italicized percentages refer to the number of cases in the first column at the same horizontal level; the rest are based upon the entire series of 200 cases.

the number of cases requiring pneumolysis of apical-cap adhesions is 37 per cent of the 38 cases having apical caps alone may be assumed to indicate the percentage of all cases with this type of adhesion in which pneumolysis is essential; that they constitute 7 per cent of the whole group of 200 cases studied is obviously a matter of chance.

On this more significant basis, pneumolysis was found to be essential in 8 per cent and desirable in an additional 22 per cent of cases with string adhesions alone; essential in 11 per cent and desirable in an additional 22 per cent of cases with bands alone; essential in 37 per cent and desirable in another 3 per cent of cases with apical-cap adhesions alone; essential in from 33 to 42 per cent, and desirable though not essential in from 11

to 16 per cent of cases with mixed adhesions. (In table 1 percentages based on the entire series of 200 cases are also given for comparison with the above percentages, which are italicized, and for comparison with figures given in the literature.)

MANAGEMENT OF ADHESIONS

Like all surgical procedures in tuberculosis, intrapleural pneumolysis has been introduced slowly and somewhat dubiously. The original technique of Jacobaeus was difficult and in some respects dangerous, and for some time only a relatively few men could perform the operation. To-day, with improvements in technique and instruments, the operation has been simplified and made relatively safe, and the number and severity of operative and postoperative complications have been very much reduced. Its field of usefulness has thus been so enlarged that, on the one hand, it may be applied to the more difficult cases, and, on the other hand, it need no longer be regarded as an emergency measure. The severance of properly selected adhesions should be no more dangerous in skilled hands than an initial pneumothorax, or a phrenic evulsion. In the light of present experience it is therefore possible to weigh other considerations than necessity in deciding for or against pneumolysis. Can convalescence be materially shortened by surgical intervention? Can positive sputum be made negative more quickly? Is the risk of operation less than the risk of passive management? In answering such questions, the practical considerations for intervention narrow down to the type of adhesion present and the mechanical opposition it appears to offer to early closure of a cavity.

The cases to be described illustrate some of these problems of management. The technique and some of the instruments used have been described elsewhere (7). In the earlier series of cases modifications of the instruments then available were developed to meet the surgical problems encountered. The most useful of these to the writer is the operating forceps-thoracoscope (figure 3) employing the vacuum-tube high-frequency machine as the source of electric current. Other modifications and adaptations of existing instruments to the problems of pneumolysis are described, together with the technique employed in the cases reported here.

The severance of strings and cords: The easiest type of adhesion to sever is the string or cord. If it is allowed to stretch sufficiently before the operation, it rarely contains important blood-vessels and almost never

For details see AMER. REV. TUBERC., 1933, xxviii, 528.

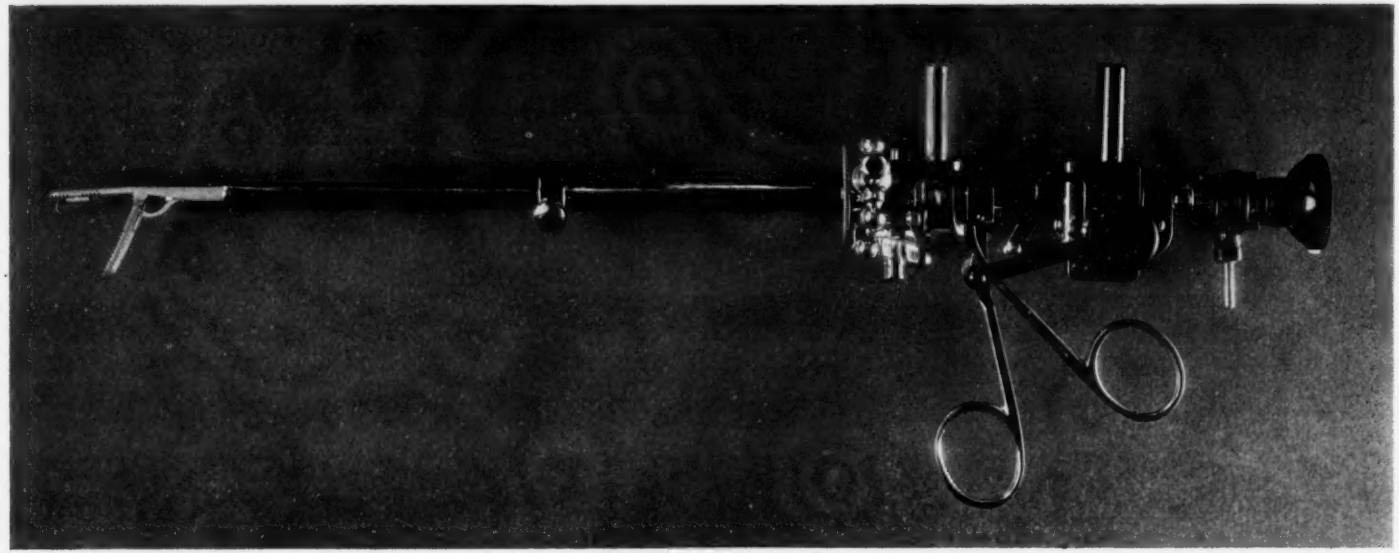

FIG. 3

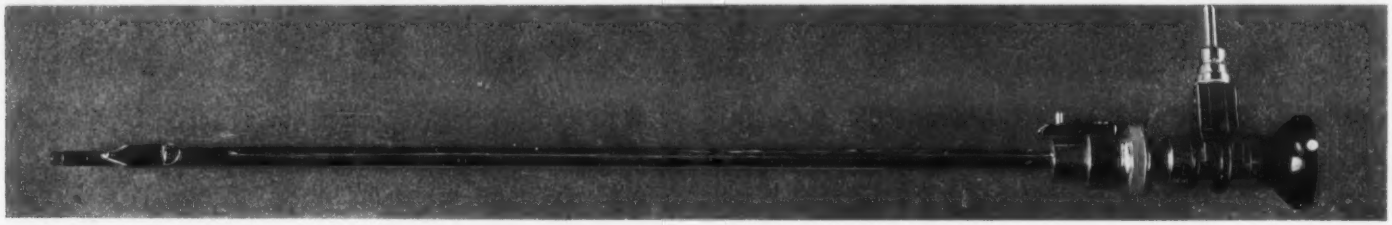

FIG. 3a

FIG. 3. Assembled operating forceps-thoracoscope, with improved diagnostic telescope (fig. 3a) for inspecting and transilluminating adhesions. For details see AMER. REV. TUBERC., 1933, xxviii, 528.

any lung substance. Only occasionally do pleural reactions of any consequence follow surgical severance with the forceps-thoracoscope. Empyema, secondary haemorrhage or spontaneous pneumothorax should not occur, if the technique has been properly followed. The indications for severing string and cord adhesions can be materially widened with considerable benefit to the patient, to include most cases in which they prevent collapse, and many in which they delay a return to health.

There is another reason for early intervention with this type. Not infrequently, as time goes on, adhesions have been known to change their anatomical appearance and, instead of stretching and becoming narrower and easier to handle, they become thicker and wider, with shortening of the adhesion and consequent expansion of the lung. Sometimes this happens without any apparent cause, but more often it follows an intercurrent pleural effusion, which may occur without warning.

Of the 78 patients in whom strings alone were found, pneumolysis was considered advisable in 23, or 28 per cent, and essential in 6, or 8 per cent.

When multiple string adhesions are present, it may be advisable not to attempt to sever all adhesions at one cutting. Postoperative reactions and consequent hospitalization in many cases can be reduced by performing the operation in stages. The same principle holds here as in thoracoplasty. Tuberculous patients can often stand considerable surgery if not too much is done at one time. The following is a case in point:

Case 2: J. S., male, 36 years of age, was diagnosed as tuberculous, November 3, 1932. At that time there was an active pathological process involving the greater part of the left lung with excavation. There was also a complicating diabetes with 250 mgm. of blood sugar, and 5 per cent sugar in the urine. Pneumothorax was instituted on November 4, 1932, and the patient responded satisfactorily. Four dense adhesions were observed, extending laterally from the upper lobe to the chest-wall. The uppermost extended to the 1st interspace, the one below this to the posterior lateral chest-wall in the region of the 2nd interspace, and the two lower ones to the lateral chest-wall in the region of the 3rd interspace. These adhesions prevented closure of the cavities (figure 4). On April 14, 1933, a closed pneumolysis was performed and two cord adhesions severed. No attempt was made to cut the other two for fear of producing too severe a pleural reaction. The patient was hospitalized only one day. The postoperative pleural reaction was mild, with a slight elevation of the temperature for three days, and a mild effusion, which did not require tapping. The cavity was reduced one-half in size and the patient's general condition improved.

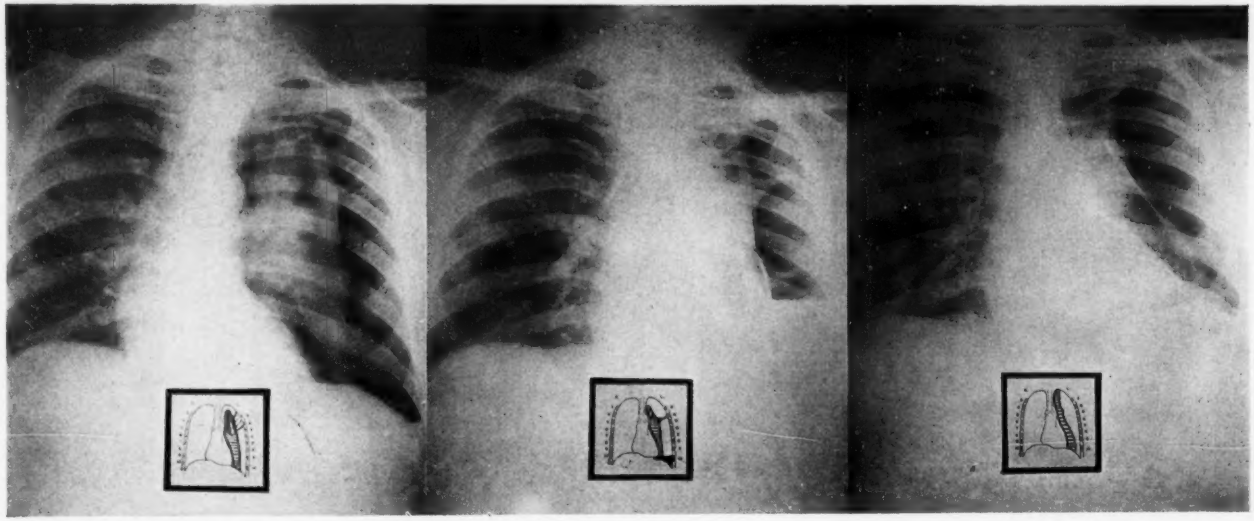

FIG. 4 FIG. 5 FIG. 6

FIG. 4. Case 2, J. S. Multiple string and cord adhesions preventing collapse of large cavity. Such cases are sometimes best managed by operating in stages in order to prevent postoperative complications and reduce hospitalization.

FIG. 5. Case 2, J. S. After first-stage pneumolysis. Although only two string adhesions were severed there was considerable postoperative reaction with effusion, largely because of the poor general condition of the patient. Any attempt to sever the remaining adhesions at the same time undoubtedly would have precipitated a more violent postoperative course.

FIG. 6. Case 2, J. S. Thick cord adhesion severed. Cavity closed. Practically no postoperative reaction following second-stage pneumolysis.

Pneumothorax refills were continued as before. After stretching a little, the remaining adhesions (figure 5) prevented further collapse, and they appeared, indeed, to be getting thicker. In view of the fact, moreover, that the patient had haemoptysis from time to time the remaining adhesions were severed October 9, 1933, six months after the first stage. There was even less reaction from this operation than after the first, and the cavity promptly closed (figure 6). The patient is now in excellent health and works every day.

Both stages of pneumolysis were accomplished with only two days' hospitalization, thus conserving the patient's financial resources and eliminating long periods of invalidism from severe postoperative complications. It is apparent also that the cavity could not have been closed by any other method.

The severance of band adhesions: It is sometimes possible to sever band adhesions as readily as strings or cords, or they may be so troublesome that the remedy is worse than the disease. It seems to me that the determining factor is the length of the adhesion from the chest-wall to the lung. When the adhesion is short it not infrequently contains lung substance, which the operator, however careful, may easily cut into. This is particularly characteristic of apical adhesions that run for a considerable distance along the inner surface of the first interspace with their length varying from point to point. Often a pleural reaction of considerable severity and of prolonged duration may follow the severance of such adhesions from their parietal attachment.

Nevertheless, the problem may be solved with comparative ease and safety if two rules are observed. The *first* is not to attempt surgery until the adhesion has had time to stretch spontaneously. How long to wait is of course a matter of judgment based upon clinical experience. In my cases, from three to six months have often elapsed before adhesions of this type have presented a sufficiently good, though not necessarily ideal, line of attack to the forceps-thoracoscope.

The *second rule* to bear in mind is that it is usually not necessary to sever all adhesions in order to close a cavity completely, and not always necessary to cut through all of one adhesion. They often yield surprisingly once they have been weakened sufficiently by electrosurgery. When the point of greatest tension has been released, properly spaced pneumothorax refills will in time accomplish the desired results.

Analysis of the mechanical factors involved from careful fluoroscopic and X-ray studies of the case is of course necessary to a decision. Usually it is possible to determine with relative accuracy at what point on

the wall of the cavity the tension must be released to permit collapse. Usually when there are several adhesions at least one must be severed, whereas the others may or may not be cut at the discretion of the operator. To prevent cutting lung substance the adhesion may be transilluminated with the special diagnostic telescope (figure 3a), by means of which a lamp on an extension can be inserted on the opposite side of the adhesion.

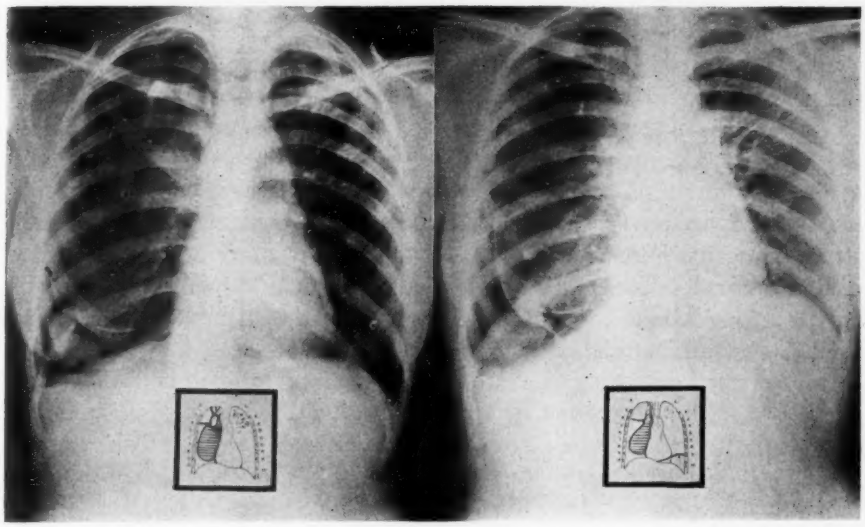

FIG. 7 FIG. 8

FIG. 7. Case 3, M. R. Large cavity in right upper lobe prevented from collapsing by several apical band adhesions and one lateral string. The patient was in poor general condition and only the nearest band was severed, in order to collapse the cavity with as little surgery as possible.

FIG. 8. Case 3, M. R. Cavity closed after severing the nearest band adhesion. The lateral string stretched readily as anticipated and did not delay closure. A phrenic crushing and scaleniotomy was performed on the left side, and all symptoms promptly disappeared.

Case 3: M. R., white, female, 23 years of age, was diagnosed as tuberculous in May, 1932. At that time she had positive sputum with disease in both upper lobes, more marked in the right with cavity-formation. She immediately went to a sanatorium in the Southwest, where she followed medical instructions faithfully without making progress. On November 4, 1932, pneumothorax was instituted in the right side. Because of financial conditions the patient was forced to return East. I first saw her on May 24, 1933. At that time she weighed 103 lbs., her sputum was positive, and there was considerable cough

and expectoration. Blood sedimentation was rapid, represented by a diagonal curve with an index of 24 mm., denoting moderate activity of the pathological process. A careful study of the X-ray plates of her chest revealed a large and uncollapsed cavity in the right upper lobe held out by adhesions (figure 7). One of these, band-like in appearance, extended from the upper part of the collapsed lung to the lateral chest-wall following the contour of the 1st rib. The other adhesion, string-like in appearance, extended from the junction of the upper and middle lobes to the lateral chest-wall in the region of the 2nd interspace. There was considerable exudative infiltration with two small cavities in the upper lobe of the left lung.

It was evident that in spite of the advantages of climate and altitude and sanatorium care, the patient was much worse than when first diagnosed, largely because of the uncollapsed cavity. Because of her poor clinical condition it was important to do as little surgery as possible and yet to close the cavity promptly. Careful study of the X-ray films showed that it was necessary to weaken the wide band attached to the 1st rib sufficiently to permit stretching. Accordingly, July 14, 1933, I severed one inch of the free border of this band adhesion along its parietal attachment. No effort was made to cut the string adhesion. The patient stood the operation well. There was some postoperative reaction for a few days, but no effusion. The patient began to improve by the end of the first week after the operation, the cough and expectoration decreasing by about 50 per cent. On October 30, 1933, I crushed the phrenic nerve and performed a scaleniotomy on the left side to help that lung, which was showing further extension of the disease. All symptoms promptly disappeared. The patient now weighs 121 lbs. The large cavity on the right is closed (figure 8). The string adhesion that was not severed stretched readily under the pressure of the pneumothorax. The cavities in the left lung closed. It is likely that a severe pleural reaction, probably with fatal result, would have followed any attempt to sever the entire band adhesion and the string adhesion at one cutting. The patient is now contemplating marriage.

It is interesting to compare the progress of this patient under climate and altitude and sanatorium care, with an unsatisfactory pneumothorax, with the success of modern collapse therapy, carried out at home under unfavorable conditions in the heart of an Eastern city.

Case 4: A. P., male, white, 46 years of age, was diagnosed as tuberculous, May 1, 1933. At that time there was a fairly large cavity in the right upper lobe. Pneumothorax was instituted, May 15, 1933, and a good separation obtained. The cavity, however, could not be collapsed because of at least three adhesions seen in the X-ray film. The most troublesome was a laminated broad band

about 2½ in. wide at its base, extending from the apex of the lung to the apical pleura and also along the 1st rib. The other two were of the cord variety and extended laterally to the 1st and 2nd interspaces respectively. On August 23, 1933, the two cord adhesions and at least two-thirds of the broad adhesion were severed at one operation with the forceps-thoracoscope. The patient apparently was not distressed by the operation and was in splendid condition after an ordeal of an hour and a half. There developed, however, a severe pleural reaction, which persisted with varying severity for almost four months. The patient, of course, was confined to bed, and at least four tappings were made before the acute pleurisy subsided. The cavity, however, closed within two months after the operation and the patient is now in excellent condition. In retrospect it appears that the pleural reaction with its prolonged invalidism could probably have been prevented by performing the operation in at least two stages and severing less of the broad adhesion. There is an added danger, following such pleural reaction, of expansion of the lung with loss of the pneumothorax.

The severance of apical caps: Apical-cap adhesions account for at least 50 per cent (19 out of 36 cases) of all uncollapsed cavities. They are the most troublesome and most dangerous type of adhesions to sever, and it is questionable whether internal pneumolysis is the procedure of choice in every case. In the first place some of these adhesions are attached to the very apex of the pleura, and are difficult to reach. In the second place they often overlie stiff-walled cavities, which have existed for years, with the parietal pleura or cap making up part of the cavity-wall. The danger of empyema, of marked pleural reaction, of spontaneous pneumothorax, is greatly increased. Even if the adhesion can be severed successfully the operation must be done in stages, and success is achieved only after expenditure of much time and effort. Some of these patients would seem to be better subjects for partial thoracoplasty or external pneumolysis and *plombage.* However, if the latter are contraindicated an attempt at closure of such cavities should be made by internal pneumolysis provided one recognizes the mechanical difficulties involved. I have obtained the best results in my cases by being content at each stage of the operation to sever perhaps a half-inch of the free edge of the adhesion, and allowing sufficient intervals between operations for the pneumothorax to stretch the rest of the adhesion. Sometimes the operator is rewarded with a brilliant result in an apparently hopeless problem (figures 9 and 10).

This type of adhesion also involves other difficulties that are not

encountered with strings or cords. Most of the cutting must be done along the parietal pleura, causing pain unless the pleura can be thoroughly anaesthetized beforehand. Figure 11 illustrates a needle for anaesthetizing the pleura under thoracoscopic control. The end of the needle, being curved, is always in full view, for ease in manipulation.

Another problem is the difficulty of grasping the adhesion within the jaws of the forceps-thoracoscope in many cases because there is not suffi-

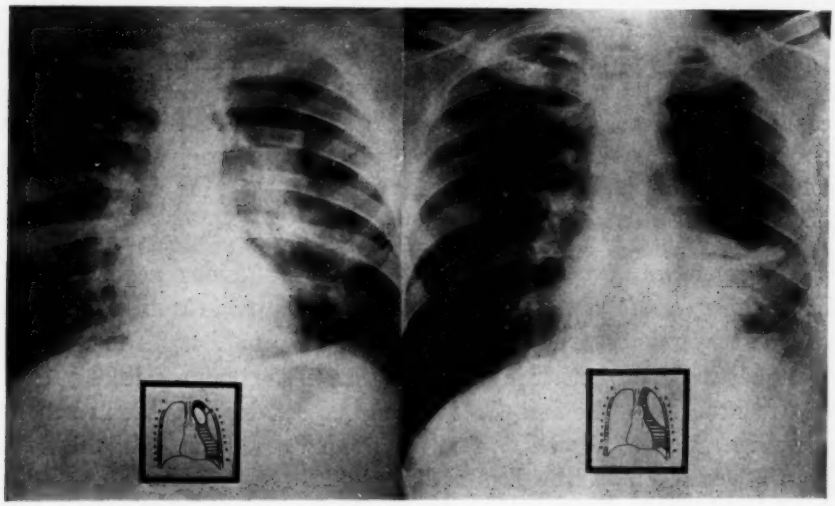

FIG. 9 FIG. 10

FIG. 9. C. B., male, white, 25 years old. Far-advanced tuberculosis, involving both lungs, with large cavity in left upper lobe, which was prevented from closing by apical cap and string adhesion. Apical caps are the most difficult and the most dangerous type of adhesion to manage.

FIG. 10. C. B. The large cavity closed after cutting the string adhesion and the free edge of the apical cap for a distance of one centimetre. The rest of the cap yielded readily to the pressure of the induced pneumothorax.

cient space between the lung and the chest-wall. Figure 12 represents a variety of coagulating and cutting electrodes that were designed to overcome this difficulty. These electrodes can be made of various design; only experience at the operating table can show which will prove most practicable. All of them fit into the general utility carrier (figure12f), which is equipped with a telescope and light. With the use of these electrodes the adhesion is enucleated at its parietal insertion into the thoracic wall after the manner of Maurer (8).

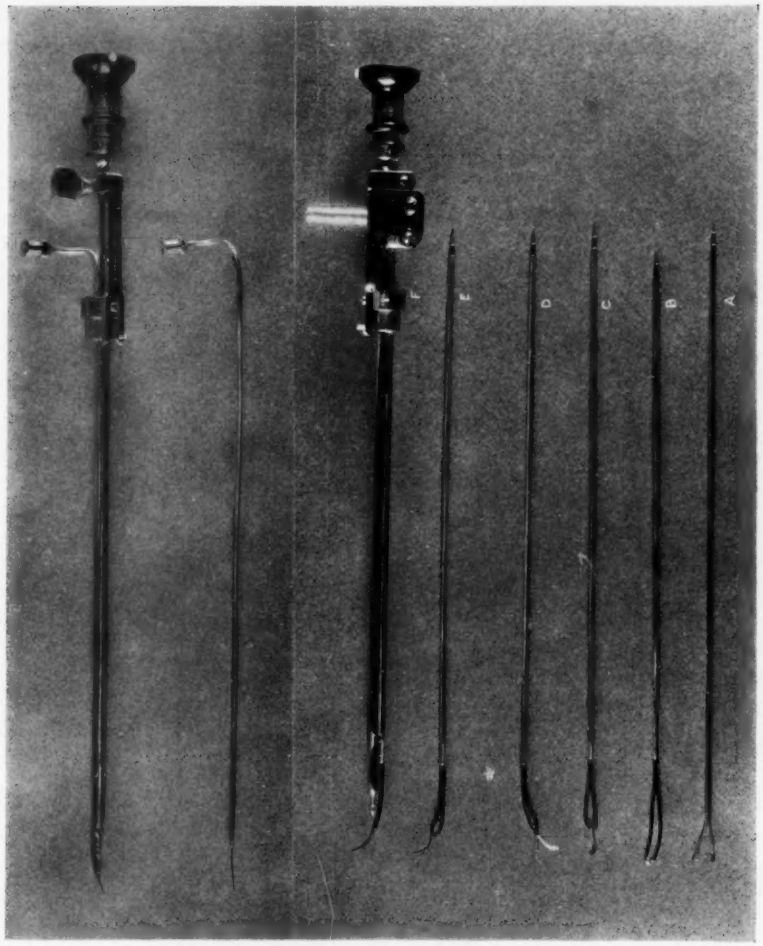

FIG. 11 FIG. 12

FIG. 11. Needle for anaesthetizing the parietal pleura under direct thoracoscopic control, used with apical caps and short adhesions.

a. Assembled needle unit, consisting of needle, needle-carrier and telescope. The point is guarded within the sheath when not in use. The needle is curved to bring the point into full view of the operator.

b. Extra needle.

FIG. 12. Sponge-carrier, coagulating and cutting electrodes, and utility carrier.

a. Carrier for introducing a gauze sponge intrapleurally under thoracoscopic control.

b. Coagulating electrode, especially useful to prevent oozing.

c, d, e, f. Cutting electrodes for apical-cap adhesions, which may be of various designs, to meet individual problems.

f. Utility carrier, with telescope and cutting electrode in place. All of the instruments fit into the utility carrier, and their working-ends are curved to permit good vision.

Another instrument for the same purpose but permitting angle variation is the thoracotome (figure 13). This instrument has also been

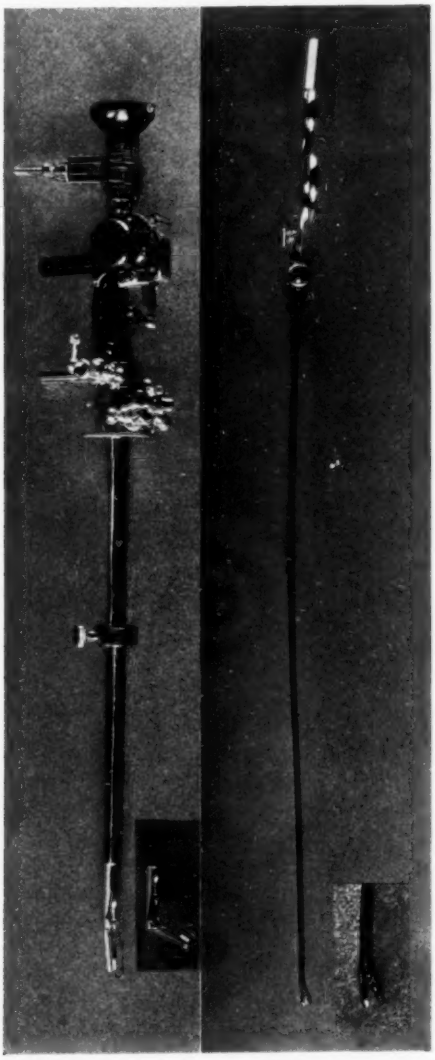

FIG. 13 FIG. 14

FIG. 13. Thoracotome for cutting broad adhesions and others too difficult to grasp within the jaws of the forceps thoracoscope. The operating end is capable of angle variation within 90°, with synchronous retraction of the telescope permitting full view of the electrode and operating field.

FIG. 14. Haemostatic forceps for grasping and coagulating bleeding stumps.

found useful for other types of adhesions too difficult to grasp with the forceps-thoracoscope.

Figure 12a illustrates a sponge-carrier for cleaning the operating area of blood should the need arise. This instrument fits into the utility carrier and is easily manipulated under the direct vision of the operator.

The severance of adhesions may in a few cases give rise to troublesome bleeding in spite of all precautions. Figure 12b shows a ball-electrode for controlling bleeding when no stump can be grasped. When it is applied to the bleeding surface haemorrhage will stop instantly. Figure 14 illustrates a haemostatic forceps for grasping and coagulating a bleeding stump.

It will be noticed that the cutting electrodes, the ball-electrode and the sponge-carrier all have their working ends curved to bring them into the full view of the operator through the telescope for greater ease in manipulation.

It is evident that it is not always possible to determine beforehand, even after the most painstaking X-ray and fluoroscopic study, whether a given adhesion is or is not suitable for operation. In such cases of doubt it is often rewarding to look into the chest with the diagnostic thoracoscope and study the mechanical problem directly. Thus, with but slight inconvenience to the patient, the thoracic surgeon can convince himself that the adhesion is inoperable, or he may find it possible to obtain a complete collapse in cases that would otherwise appear unsuitable (Welles (9)).

There is little doubt that, as we accumulate more and more experience and as technical difficulties are surmounted with the development of new and better instruments, many adhesions that prove troublesome to-day will be a matter of routine surgery in the future.

SUMMARY

Adhesions were found in 173, or 86 per cent, of 200 consecutive cases of pulmonary tuberculosis with a satisfactory pleural space for artificial pneumothorax.

A review of the 173 cases shows that in 36, or 18 per cent of the entire series, the adhesions were of such a nature as to prevent collapse, after allowing for the possibility of closing cavities by phrenic evulsion or scaleniotomy, and by spontaneous stretching of adhesions.

A more critical study of this material shows that in at least 27 more cases, or an additional 13.5 per cent of the 200 cases, pneumolysis, though

not so urgently indicated, saved or would have saved the patient considerable invalidism and expense. Moreover, in many cases it was the safer form of management. Thus, in this series pneumolysis was considered as indicated in every third case suitable for pneumothorax therapy, to promote a surer and an earlier return to health.

The management of various types of adhesions is discussed, with the indications and contraindications for surgery. Pneumolysis was essential to collapse cavities in 8 per cent of cases having string adhesions alone, in 11 per cent of those with band adhesions alone, in 37 per cent of those with apical-cap adhesions alone, and in from 33 to 42 per cent of those with mixed adhesions, and was considered desirable though not essential in additional percentages. These figures more exactly indicate the frequency with which the operation is indicated than figures based upon a given series treated by artificial pneumothorax, which will include various types of adhesions corresponding with the relative severity of the various cases included.

Closed pneumolysis can now be performed with relative ease and safety, and its field can be so extended that, on the one hand, it can be applied to the more difficult cases, and, on the other hand, it need no longer be regarded as an emergency measure.

Cases are analyzed from these points of view. Some modified instruments are described and illustrated, among them a thoracotome and various types of cutting and coagulating electrodes for apical-cap adhesions, a needle for anaesthetizing the pleura under thoracoscopic control, a ball-electrode to control oozing, a haemostatic forceps to grasp and coagulate bleeding stumps, and a sponge-carrier for keeping the operating field clean and dry.

Acknowledgment is made to Miss Eleanor S. Cooper of the Henry Phipps Institute for editorial assistance.

The instruments described were made for the writer by The American Cystoscope Makers, Inc., New York.

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INTRAÄBDOMINAL PRESSURE AND ITS REGULATION

DAVID SALKIN[1]

The term *intraäbdominal pressure* is widely used despite the meagre literature on the subject. The works of Coombs, Waggoner and Overholt are most outstanding, and merit attention, although in our clinical experiences with intraperitoneal air-inflations the complexity of pressure readings and some observed phenomena cannot be explained by the literature dealing with the subject.

In 1920, Helen Coombs (1) published her findings on the influence which intraperitoneal water-injections exerted on the intraäbdominal pressure under normal and abnormal conditions. Plotting the pressure-volume results she obtained hyperbolic curves in which the pressure-rise was slow at first and then became more rapid. She concluded that the results demonstrated the reflex tone of the abdominal muscles or the "postural activity of Sherrington."

Waggoner (2), in 1926, stated that changes in intraäbdominal pressures were due to variations in the size of the cavity induced by the character of respiration, tone of the abdominal wall, position of the abdominal viscera and posture. In an extensive series of investigations he demonstrated a subatmospheric pressure to be present in the normal peritoneal cavities of both living and dead subjects.

Overholt (3), in 1931, repeated the experiments of previous authors. He found the intraperitoneal pressure to be extremely variable; that in quiet respiration in dogs the abdominal pressure was less during inspiration; that posture was an important factor; and that air may be introduced intraperitoneally without a corresponding rise in pressure.

INITIAL INTRAPERITONEAL PRESSURE

In the *living animal* peritoneal pressures may be obtained by means of a manometer graduated in millimetres of water. Determinations made after the injection of novocaine into the peritoneal cavity, the use of faulty stop-cocks and connections, or connecting the manometer to the needle after its insertion may give atmospheric or positive pres-

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sures. Faulty methods such as these resulted in the readings shown in table 1. Careful injection of novocaine, so that it does not reach the peritoneal cavity, and the use of a closed-air system gave pressures which were subatmospheric (table 2). Grouping these figures on the basis of pressure incidence gives the percentage results shown in table 3. In a series of 50 human cases only one showed an atmospheric pressure, 60 per cent showed a pressure from zero to minus 10-mm. water, and 88 per cent from zero to minus 30-mm. water. Rabbits, in which no

TABLE 1

Intraperitoneal pressures obtained with faulty technique

PRESSURE: MM. WATER	NUMBER OF CASES
0	19
+1	1
+2	2
	22

TABLE 2

Intraperitoneal pressures obtained with correct technique

PRESSURE: MM. WATER	NUMBER OF CASES
0	1
−1	3
−2	7
−3	4
−5	3
−10	5
−20	8
−25	4
−30	2
−40	3
−50	3
	50

anaesthesia was used, gave similar results, although high negative readings were rare (table 4).

In a series of 20 dead human subjects who showed *no evidence of abdominal disease,* subatmospheric readings were obtained (table 5). In most of these cases, readings were taken within 10 minutes postmortem and in all cases within 30 minutes, and before *rigor mortis* had set in.

Individuals dead with *abdominal disease,* such as tumors, adhesions or

fluid, may show variable pressures. High positive readings are obtained only with massive changes in abdominal content. The pressure may even vary in different areas of a free peritoneal cavity, and is usually a higher negative in the epigastrium than in the hypogastrium. One case with a small pelvic effusion showed a minus 2-mm. water-pressure in the epigastrium and a plus-10 mm. water-pressure in the hypogastrium.

TABLE 3

Grouping of cases in table 2

GROUP	PRESSURE: MM. WATER	NUMBER OF CASES	PER CENT
1	0 to −10	30	60
2	−10 to −20	8	16
3	−20 to −30	6	12
4	−30 to −40	3	6
5	−40 to −50	3	6
		50	100

TABLE 4

Intraperitoneal pressures in rabbits

PRESSURE GROUP: MM. WATER	PER CENT
Atmospheric	0
0 to −10	60
−10 to −30	40
	100

TABLE 5

Intraperitoneal pressures in dead human beings within 30 minutes after death

PRESSURE GROUP: MM. WATER	NUMBER OF CASES	PER CENT
Atmospheric	0	0
0 to −10	14	70
−10 to −40	6	30
	20	100

From the above observations one may conclude that support must be given to Waggoner's contention and that the pressure in the normal peritoneal cavity is always subatmospheric in the living or dead animal; in the "pathological" cavity it varies. All the above readings were made on the human being or laboratory animal in the dorsal position only.

INTRAPERITONEAL PRESSURE CURVE

If air or water be slowly injected into the peritoneal cavity and simultaneous pressure-readings taken, a hyperbolic curve is obtained, in which the rise is slow at first and then rapid. But, if one waits for several minutes after each unit volume of air is injected, it is noted that the pressure drops to a low level; and if another increment of air is injected, there is again a primary high reading which falls gradually to a low level. Each volume of air injected is associated with a high primary

TABLE 6

*Typical experiment showing abdominal accommodation**

Experiment 2; Rabbit; male; weight 2,500 gm.; dorsal position; no anaesthesia

AIR INJECTED	PRIMARY PRESSURE: MM. WATER	FINAL PRESSURE: MM. WATER	RESPIRATION	STATE OF ABDOMEN
cc.				
Initial	−10	−10	90	
100	+12	+5		
200	47	8		
300	70	14		
400	60	10	120	Soft
500	120	10		
700	297	0		
900	270	0	Costal	Tense
1100	135	110		
1300	216	0		Soft
1500	512	10		
1600	540	30		
1800	600	15	Labored	Tense
1900	600	60	56	
2000	620	0	20	

* When the experiment was stopped and the animal freed it resumed its normal conduct with no apparent ill effects.

reading and a low final reading. When the high primary readings are joined on a volume-pressure graph a definite curve is obtained; the low points when joined produce a curve of a different nature. In further discussion the former will be designated as the Primary curve and the latter as the Secondary or True curve.

As air is injected, the primary curve rises slowly at first and then more rapidly, producing a rough *hyperbola* up to a certain point. The curve may be gradual or steep in its rise depending upon the rapidity of inflation. At a given point it drops suddenly to a low level and with fur-

ther inflation rises again in a roughly hyperbolic manner but on a new level. There may be one or more such drops before the animal shows collapse and what is termed the "breaking point." Just before each drop the abdomen becomes tense and respiration labored; after the drop, it becomes soft and the respiratory embarrassment subsides.

The true curve has its range at (or slightly above) atmospheric pressure, and with one exception shows no characteristic changes. Coincident with the sharp fall of the primary curve there is a sharp rise of the true curve, and when the former rises again the latter falls to its usual

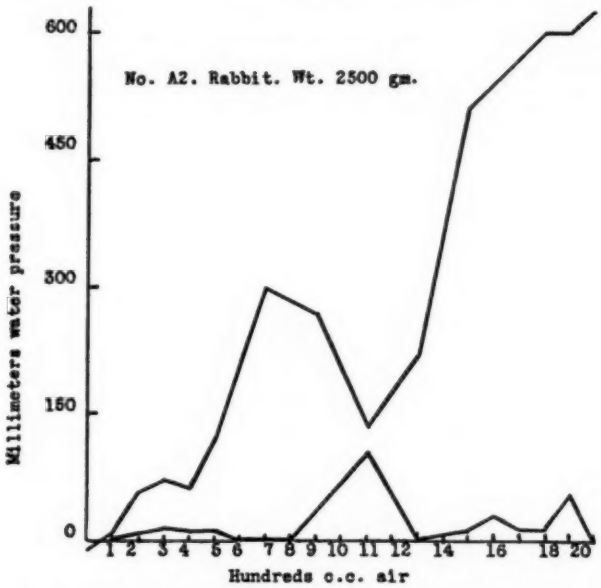

FIG. 1. ABDOMINAL ACCOMMODATION SHOWING PRIMARY AND TRUE CURVES AND TONUS ADJUSTMENT PHASE

low level. When the "breaking point" of the animal is reached the true curve rises sharply to meet the primary. Table 6 shows a typical experiment, and figure 1 its graphic representation.

SIGNIFICANCE OF THE PRESSURE CURVE

The secondary curve is the true one because it gives the final pressure existing in the abdomen; and since its range is near zero for all volumes of air injected one must infer the presence of a process of *abdominal accommodation*, which maintains a near-atmospheric pressure at all vol-

umes. The process must be regarded as a function of muscular activity; when air is introduced intraperitoneally, the added content gives rise to a high pressure, but the muscle quickly relaxes to reduce this pressure.

With continued abdominal inflation a point is finally reached at which the abdomen becomes tense, the primary curve falls and the true curve rises. It would be expected that further inflation would increase the tension and the true pressure readings, but, instead, the abdomen becomes soft again, the primary curve rises, the true curve falls and the animal is in a better general condition. There must have occurred at this point some method of muscular adjustment which enables the abdomen to maintain further increases of air at zero pressure; the change is probably one of muscle tension and will be designated as the *Tonus Adjustment Phase*. There may be several such phases before the "breaking point" is reached. This change in tension may be regarded as a further means of abdominal accommodation.

Why there should be such a process as abdominal accommodation is problematical. The digestive tube, bile-ducts, liver, kidneys, pancreas and other organs function normally under mild positive pressures while the cavity surrounding these organs must have a lesser pressure to enable proper visceral activity. It is probable, then, that a near atmospheric peritoneal pressure is essential for the proper action of abdominal viscera; and one of the vital properties of the abdominal wall is its adaptability in maintaining a near-zero pressure under varying conditions.

FACTORS IN ACCOMMODATION

There are two important factors involved in the process of accommodation, namely, the time element and the mechanism of muscle relaxation and contraction.

Whether the abdominal musculature lengthens actively or is passively stretched is shown by a study of tables 7 and 8. If air is removed from an abdomen at zero pressure one would expect a negative pressure to result; but this does not occur. The removal of air produces an immediate sharp rise in pressure which gradually falls again to zero. Apparently the muscle fibres contract to accommodate the lessened abdominal content, and do so excessively at first. This is followed by a relaxation just sufficient to maintain the air at zero pressure. If the same experiment is performed after the last tonus adjustment phase, the final pressure both after inflation and removal of air is kept at a minimum above at-

mospheric. Such a rapid adjustment of intraperitoneal pressure can depend only upon a neuromuscular mechanism and is not influenced by posture or respiration. One may therefore conclude that since there is a rapid adjustment of the abdomen to maintain a zero pressure both on addition and removal of abdominal air content, the process of accom-

TABLE 7

Activity of accommodation process

Human adult male. During a pneumoperitoneum air was removed and replaced

VOLUME AIR	PROCEDURE	PRIMARY PRESSURE: MM. WATER	TRUE PRESSURE: MM. WATER
cc.			
900	Injection	20	0
1000	Injection	20	0
1100	Injection	20	0
1200	Injection	22	0
1100	Removal	25	0
1200	Injection	22	0
1300	Injection	22	0
1400	Injection	28	0

Note that on removal of air the pressure became positive and then went down to atmospheric.

TABLE 8

Activity of accommodation process

Rabbit: male; weight 2,000 gm.; dorsal posture; no anaesthesia. Primary injection of air at rate of 10 cc. per second till 1,000 cc. air was in abdomen.

VOLUME AIR	PROCEDURE	PRIMARY PRESSURE: MM. WATER	TRUE PRESSURE: MM. WATER	ACCOMMODATION TIME
cc.				*minutes*
1000	Injected	162	0	15
800	Removal	40	0	6
1000	Injected	40	0	4
800	Removal	30	0	6
1000	Injected	58	0	10

modation is an active one in both phases of muscle contraction and relaxation.

The time required for the primary reading to reduce to the true reading is variable but characteristic when graphically represented. Table 9 gives the results of a typical time-accommodation experiment and figure 2 its graphic representation. The time curve at each volume of air is roughly hyperbolic in nature, with a rapid initial fall and a slower sub-

sequent descent. Occasionally, a curve may show a small plateau in its downward course. At the tonus-adjustment phase the descent is hyperbolic until a constant level is reached. These characteristics are present whether the curve is large or small and they represent the mode of muscle relaxation. After a change in volume the muscle fibres relax quickly at first and then more slowly till the true reading is reached, and the higher the primary reading the greater is the initial relaxation.

TABLE 9

Typical experiment showing accommodation time

Rabbit: male; weight 1,350 gm.; dorsal posture; no anaesthesia; initial pressure: −20 mm. water

MINUTES	PRESSURE IN MM. WATER UNDER EACH VOLUME AIR IN CC.						
	100	200	300	400	500	600	700
0	40	140	200	162	300	160	220
¼			160		189		150
½	36	110	70	150	150	110	135
¾			66		112		80
1	24	90	56	135	76	78	70
1¼					70		
1½	18	72	S		66		62
1¾			T		64		
2	12	56	R	110	64	72	64
2½	8	46	U				
3	6	36	G	94	58	66	64
3½	2	30	G				
4		22	L	92	58		58
4½	0	16	E				
5		14	D	90	46	40	54
5½		10					
6		8		106	24	18	54
6½		6		104			
7		2			14	16	54
7½		1					
8		½		104	6	8	54
9				104	4	2	54
10		0		104	2	0	54
11					0		

FACTORS INFLUENCING PERITONEAL PRESSURE

The main factors influencing peritoneal pressure are the rate of injection of air or water, posture of the animal and respiration.

The *rate of injection* has a marked effect upon the shape of the primary curve; the secondary curve does not change. Figure 3 reveals that the more rapid the injection the higher is the level of the curve and

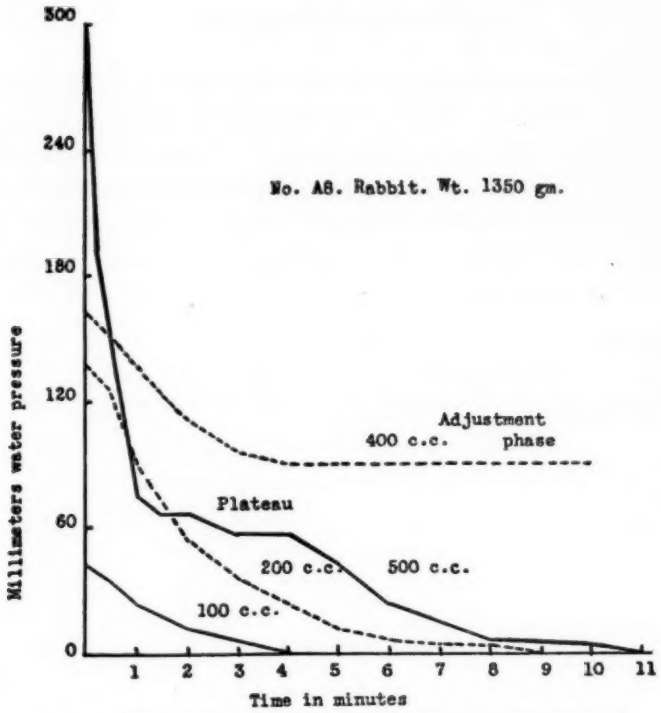

FIG. 2. TIME-ACCOMMODATION CURVES AT VARIOUS VOLUMES

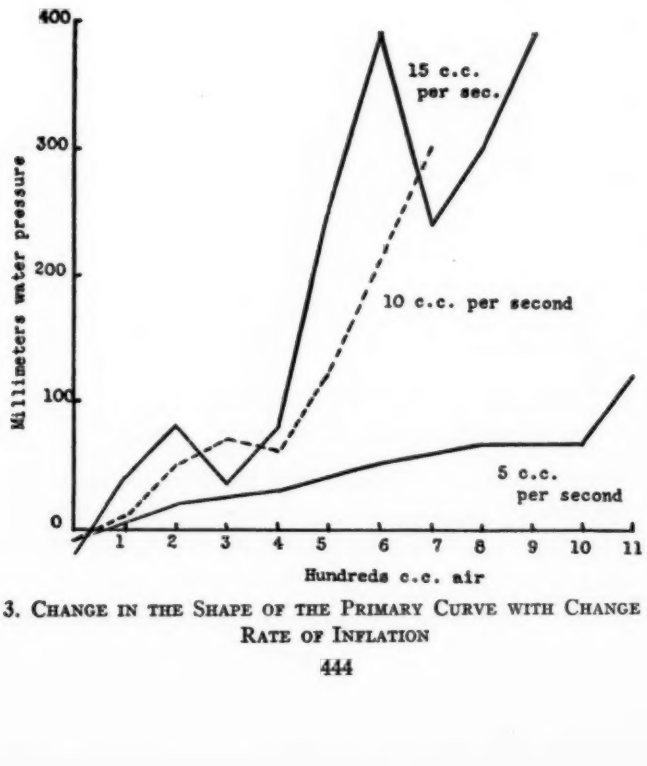

FIG. 3. CHANGE IN THE SHAPE OF THE PRIMARY CURVE WITH CHANGE IN THE RATE OF INFLATION

the more frequent are the adjustment phases. If the injection is extremely rapid the curve may approach a vertically straight line, and if extremely slow a horizontally straight line. Theoretically, the primary curve may vary from the horizontal to the vertical, but practically it lies somewhere between these extremes. Since the true curve does not change with the variation of the injection rate it is the only one of importance.

Posture plays an important part in changing initial intraäbdominal pressure. In the dorsal position the pressure is always subatmospheric, but, as shown by Overholt, in other positions the pressure may become positive even with a relaxed musculature. In the dorsal position, the pressure is less in the epigastrium than in the hypogastrium. In the

TABLE 10

Effect of posture on intraäbdominal pressure

POSITION	DORSAL	HEAD-UP	HEAD-DOWN	SUPINE
Rabbit 102				
Epigastric	−10	−20	+16	−2
Hypogastric	0	+12	−30	+2
Rabbit 103				
Epigastric	−28	+4	+26	0
Centre	−24	+8	+24	+24
Hypogastric	−20	+20	−30	−26

"head-up" position, the viscera tend to fall, the hypogastric pressure rises and the epigastric falls giving a mean atmosphere pressure. In the "head-down" position, the viscera fall toward the epigastrium, increasing the pressure there and lessening it in the hypogastrium, resulting again in a mean atmospheric pressure. In the supine position, the pressure is usually negative but may even be positive, especially about the central abdominal area (table 10).

The effect of respiration upon peritoneal pressure was first properly shown by Overholt. It was at first poorly demonstrated because coarse U-tube manometers were used, but with patient work a fine U-tube manometer will demonstrate all pressure changes. All human subjects, rabbits and cats showed a greater pressure on inspiration than on expiration and the difference in all animals varied from 0.5 to 5 mm. water.

After the injection of air the respiratory oscillations become very evident, but too much reliance should not be placed on these readings, for the introduction of a foreign-body may produce a new readjustment of the relation between the action of the diaphragm and of the abdominal wall.

In rabbits it is very difficult to paralyze the diaphragm even with large amounts of air, and when it is paralyzed signs of respiratory failure quickly supervene. In a rabbit upon which a bilateral phrenicectomy was performed, respirations became gasping in character and the animal lived only 3 hours. In the human subject, oscillations usually become marked at about 300 cc. air when there is produced a free layer of air between diaphragm and needle. There is a greater pressure on inspiration with a difference of 5 to 30 mm. water between the two phases, depending upon the amount of air introduced. Here again the introduction of air apparently disrupts the almost perfect mechanism which permits the abdominal wall to relax sufficiently on diaphragmatic descent, and the values obtained are much higher than those prior to air inflation.

Occasionally, when large amounts of air are used, the pressure may be less on inspiration—the so-called "paradoxical oscillation." In these cases, fluoroscopic examination reveals an apparently paralyzed diaphragm with paradoxical motion. On inspiration, this diaphragm is pulled up by the increasing negative pressure in the chest, the abdominal cavity is enlarged and its pressure is decreased. Such a state may be changed by assuming a different posture, coughing or sneezing. If the needle is placed just under the diaphragm, the pressures are of a high negativity and fluctuate with respiration, but inversely to those in the pleural cavity.

RÔLE OF COMPONENTS IN ACCOMMODATION

Accommodation is a rapid efficient phenomenon brought about by the combined nervous and muscular systems. The part played by each may be determined by the inflation of the abdomen of a recently dead animal, destruction of the spinal cord or administration of curare.

The pressure curve postmortem varies under different conditions and one may obtain three varieties of curves. One series may be obtained in an animal immediately after death when the muscle fibres are still fresh and elastic but their nervous connections are lost. The curve obtained shows only a slight rise at first and then goes up sharply (figure 4). This curve represents only muscle elasticity.

A second series is obtained by waiting for varying periods of time after death before inflating the abdomen. Depending upon the degree of *rigor mortis* there is a variable amount of muscle elasticity. When rigor is complete the abdomen acts as a rigid structure and the pressure volume graph is a straight line.

A third series of curves may be obtained after the animal has died as a result of air-inflation. In such cases the elasticity has already been ex-

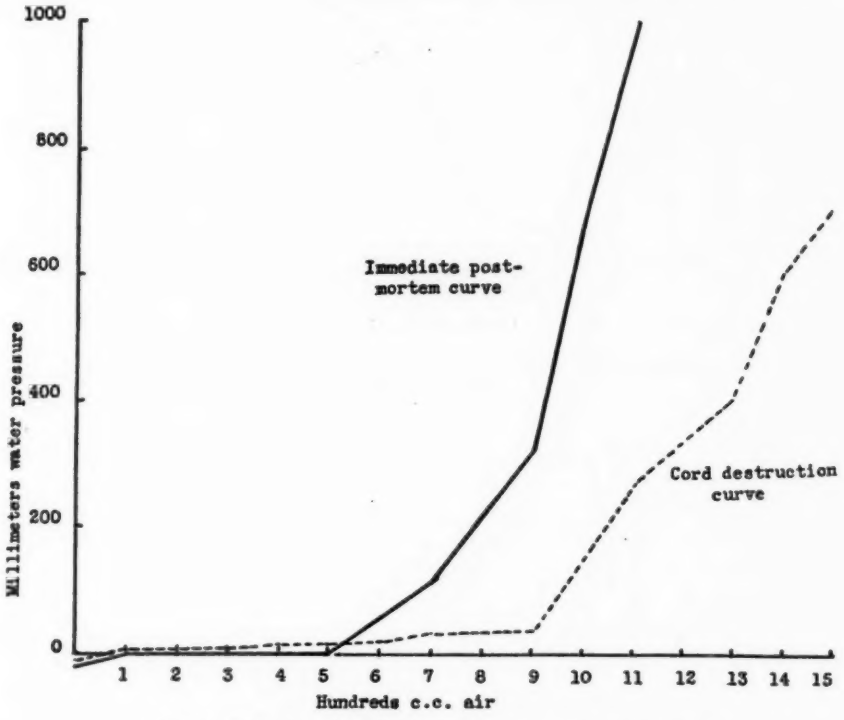

FIG. 4. RÔLE OF THE MUSCULATURE IN ACCOMMODATION

hausted and the abdomen acts as a rigid structure. The resulting graph is a straight line (figure 5).

After destruction of the spinal cord so that the animal is paralyzed from the 3rd dorsal segment down but the phrenic nerves are not affected, the curve obtained resembles the postmortem curve immediately after death. There is a slow rise at first followed by a rapid ascent.

The characteristics of both postmortem curves and those following cord destruction are:

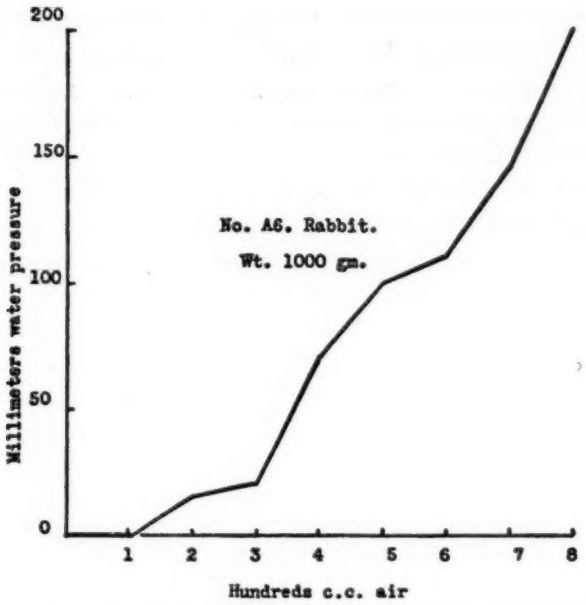

FIG. 5. POSTMORTEM CURVE IMMEDIATELY AFTER DEATH BY PREVIOUS INJECTION OF 1000 CC. WATER

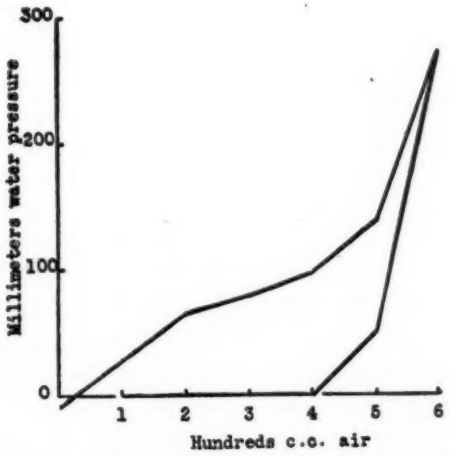

FIG. 6. WATER CURVE SHOWING ACCOMMODATION

(1) Only one set of readings is obtained; there is therefore no primary or true curve.

(2) There are no phases of tonus adjustment.

(3) Less air can be introduced than into the normal abdomen.
(4) There is no active accommodation (table 11). When air is removed from the abdomen the pressure is lessened, as in a rigid container. There is no primary increase as in a normal abdomen; and even negative pressures may be obtained on removal of air.

TABLE 11

Typical experiment showing lack of active accommodation in a dead animal
Rabbit: female; weight 1,800 gm. Death by strangulation and immediate air inflation

VOLUME AIR	PROCEDURE	PRESSURE: MM. WATER
cc.		
600	Inflation	55
700	Inflation	110
800	Inflation	220
700	Removal	160
800	Inflation	235
700	Removal	135
800	Inflation	220
700	Removal	135
800	Inflation	220
900	Inflation	320

Note that when air is removed the pressure does not increase but drops to its original level.

TABLE 12

Typical experiment showing lack of active accommodation in an animal with destruction of spinal cord

Rabbit: male; weight 2,000 gm.

VOLUME AIR	PROCEDURE	PRESSURE: MM. WATER
cc.		
1,400	Inflation	594
1,300	Removal	243
1,400	Inflation	270
1,300	Removal	81
1,400	Inflation	270
1,300	Removal	−120
1,400	Inflation	460
1,300	Removal	−27

It is to be concluded that the postmortem and cord destruction curves represent the part played by the muscle *per se* in accommodation; they feature only the factor of elasticity. Changes in tension to produce tonus-adjustment phases and the activity of the accommodation process are undoubtedly due to the nervous system.

WATER CURVES

The substitution of saline solution for air and the repetition of all the above experiments produce similar results. Coombs's curves were duplicated and found to be of a primary nature (figure 7). The water-curves show primary and true readings, activity of accommodation and a hyperbolic time-curve. Water, however, causes embarrassment and death more quickly than air. A rabbit can tolerate up to 1 cc. air per gram body-weight, but only 0.5 cc. water; respiratory failure begins to appear at slightly more than one-half of these amounts.

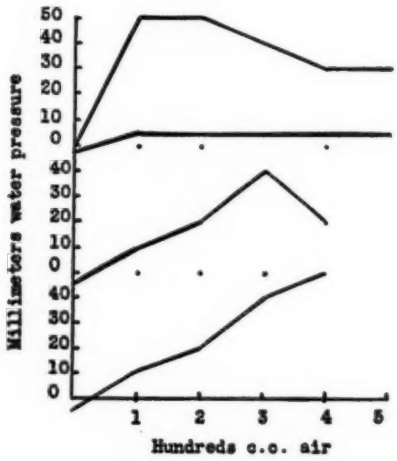

FIG. 7. FOUR HUMAN CURVES

CAUSE OF EMBARRASSMENT AND DEATH

At the injection volumes mentioned the animal begins to show rapid, shallow breathing, and on further inflation begins to gasp and ultimately stops breathing. At the stage of dyspnoea fluoroscopic examination reveals diaphragmatic paralysis with frequent powerful attempts at contraction. If at this point some air (or water) is removed the animal usually recovers. After cessation of respiration the heart usually continues to beat for several seconds and often for many minutes. Post-mortem examination reveals a normal cardiac musculature and the heart may continue to beat for several hours in normal saline or Ringer's solution.

In the human being the diaphragm may be bilaterally paralyzed and

costal respiration is sufficient to maintain life; in rabbits, costal respiration is insufficient. It is problematical whether this has any relationship to the early diaphragmatic paralysis in human beings following pneumoperitoneum and its late paralysis in rabbits. Embarrassment in the rabbit begins when the action of the diaphragm is impaired, and death occurs soon after its complete paralysis. The abdominal cavity accommodates quite as well to water as to air, but the former by its sheer weight paralyzes the diaphragm more quickly; if the rabbit is placed in the supine position more water can be injected before embarrassment occurs.

One may conclude that, contrary to some reported opinions, embarrassment and death following intraperitoneal injection of air or water is due to respiratory failure and is not of cardiac origin.

TECHNIQUE

The animal is tied securely to an animal-board, leaving the thorax and abdomen free from binders. Anaesthesia is not used in order to prevent any local or general narcotic influence on the nervous system, although under general anaesthesia both cats and rabbits give the same phenomena and results. All manipulations must necessarily be gentle, to prevent excitement and struggle.

For the inflation of air a siphon apparatus may be used (as in pneumothorax induction) with a fine water manometer graduated in millimetres. Unless otherwise stated the needle is inserted on either side of the navel, and the needles used are usually no. 19-gauge. For proper initial pressures in the human being one must obtain proper muscular relaxation and novocaine should be used only subcutaneously.

CLINICAL APPLICATION

The above findings have a direct clinical bearing on the estimation of the amount of air in the abdomen and the quantity that can be injected; the type of human curves obtained clinically; the relationship of respiration and intraperitoneal pressure; the possibility of damage to underlying viscera and the relationship of shock to abdominal pressure.

No method has yet been devised to determine the *amount of air* present in the abdomen at any given time following inflation. Due to the constant accommodation present it is evident that any one pressure-reading may denote any given volume. An index which has a limited use in the adult abdomen is to measure the total air-space between both leaves of

the diaphragm and the underlying viscera in the erect posture in the midclavicular line: a total space of 10 to 12 cm. denotes 600 to 800 cc. air. Liver dulness disappears usually at 300 cc. air and its absence in the dorsal position denotes the presence of at least 300 cc. air.

Tremendous amounts of air can be put into the human abdomen before respiratory embarrassment occurs. In one human subject a tonus adjustment phase occurred at 2000 cc. It is certainly safe to inject up to 5000 cc. air with no fear of serious consequences. In children, one may give 25 to 40 cc. air per kilogram body-weight and about one-half this amount of water.

Extensive experiments on animals and human beings indicate that it is almost impossible to *damage underlying viscera*, if ordinary precautions are used. Damage may be done, however, in cases of meteorism, urinary-bladder distention, adhesions between the gut and abdominal wall, or other abnormalities lying in the path of the needle. Joseph (4), in 1921, reported a case of death following pneumoperitoneum due to air embolus in the right common iliac artery lying in an anomalous position.

It is a common belief that the replacement into the abdominal cavity of large hernias, or the removal of large tumor masses interferes with intraäbdominal pressure to such an extent as to produce *shock* or even death. In the light of abdominal accommodation this belief is nolonger tenable. If such complications do occur they are apparently due to causes other than changes in peritoneal pressure—possibly a neurocirculatory disturbance is responsible. To produce shock by changing intraäbdominal pressure one must use such quantities of the medium as are clinically nonexistent.

RELATIONSHIP OF PLEURAL AND PERITONEAL PRESSURES

Although the peritoneal pressure shows a slight change with the phase of respiration, it is of such small value as to be almost negligible: even after inflation of large amounts of air the respiratory variations differ by only one or two centimetres water-pressure. Ordinarily the change is so slight that very fine measurements must be made to detect any difference between expiration and inspiration. We do know that there must be some respiratory change, because a barium-filled bowel moves down on inspiration, and during laparotomies the respiratory movements are marked. One must assume a respiratory adjustment between the abdominal wall and the diaphragm: when the diaphragm descends the abdominal muscles relax sufficiently to maintain an almost constant

pressure. In Overholt's dogs this process was even more effective and the pressure was less on inspiration.

Thoracic manipulations rarely affect the intraäbdominal pressure. Following phrenicectomy in human subjects or after thoracoplasty the abdominal pressure remains unchanged, and readings following inflation are characteristically the same as those in a normal subject. Readings taken in cases of unilateral phrenicectomy show a difference under the paralyzed leaf; the pressure is a higher negative on inspiration, while the other side gives reverse results, but the general abdominal pressure is unchanged. The paradoxical movement of a paralyzed leaf of the diaphragm is often ascribed to an increased abdominal pressure caused by the descent of the active leaf. Against this view are the following phenomena:

(1) There is a difference in the amount of movement between both leaves. The paralyzed leaf during a full inspiration moves up only several millimetres while the normal one moves down several centimetres.
(2) There is a difference in the time of the paradoxical movement and of the normal descent. In most cases, the paralyzed leaf rises quickly during the initial phase of respiration to its maximum height while the normal leaf still continues to descend.
(3) In bilateral phrenicectomy there is a definite paradoxical movement on inspiration. Here, the thoracic cage is the only factor involved, and certainly change in abdominal pressure is not a primary event.
(4) The respiratory change in abdominal pressure is a negligible quantity and must be insignificant for the production of paradoxical motion.

The paradoxical movement of the paralyzed diaphragm is therefore due to thoracic factors, chiefly the increased negativity during inspiration.

Although changes in thoracic volume have slight effect upon intraperitoneal pressure and accommodation, yet changes in the abdominal cavity have definite effects upon respiration. Inflation of the abdomen with air has two main effects upon pleural pressures. At first the mean pleural pressure shows a decrease in negativity which is subsequently kept at a roughly constant level upon further inflation of the abdomen. Then, following this primary change in mean pressure, there is another change with respect to respiratory rate and respiratory amplitude. The rate may increase and the amplitude would decrease or *vice versa*. There may be one or more phases of change in mean pleural pressure and one or more changes in the "rate amplitude" ratio. Apparently abdominal in-

flation produces a rapid decrease in lung-volume to a constant level associated with a change in the "rate-depth" ratio. The reason for these changes is unknown but they apparently depend upon changes in the volume. When respiratory embarrassment occurs there is a complete disruption of the rate-depth ratio and a marked decrease in lung-volume. In clinical work, abdominal inflation is seldom great enough to produce such changes, but in cases of pregnancy, ascites or tumors associated with an increased respiratory rate, this greater rate may be regarded as a phase in the "rate-depth" accommodation to maintain a constant air-intake under given conditions of activity, diet and disease.

When the abdomen is inflated with air the stretched abdominal muscles do not function so perfectly with respect to accommodation with the diaphragm, and the descent of the latter produces a slightly greater peritoneal pressure than actually occurs in the normal abdomen. Occasionally, when large amounts of air are used, the pressures may be reversed: in these cases, fluoroscopic examination reveals the diaphragm to be temporarily paralyzed and showing paradoxical motion; during inspiration the diaphragm is pulled up, enlarging the abdomen and causing a decrease in pressure. Change of position or coughing may change this "paradoxical oscillation"; the diaphragm is then found to be functioning normally again.

HUMAN PRESSURE CURVES

Induction of pneumoperitoneum in human beings has always given pressure-readings of a puzzling nature. There are several factors contributing to such a complex variety of results:

(1) Usually, inflation is not carried out sufficiently to demonstrate even the first tonus adjustment phase.
(2) The symptomatology during inflation limits the amount of air given.
(3) Such details, as waiting for true readings and controlling the rapidity of injection, are of necessity omitted in the human subject.
(4) The human subject is usually tense mentally and true muscle relaxation is seldom obtained.

However, in the human being, accommodation has been repeatedly demonstrated with its phases of primary and true readings, time-curves, tonus-adjustment phases, and the activity of the process. In all cases, the results obtained were similar to those obtained in animals under better experimental control. The curves obtained clinically during

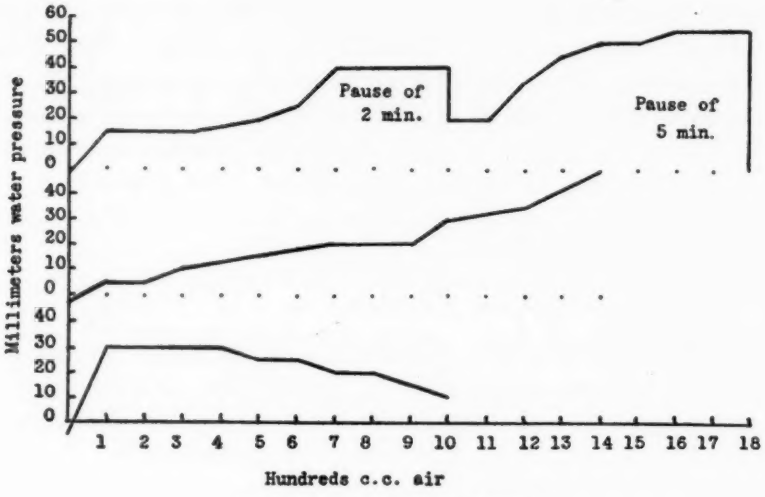

FIG. 8. THREE HUMAN CURVES

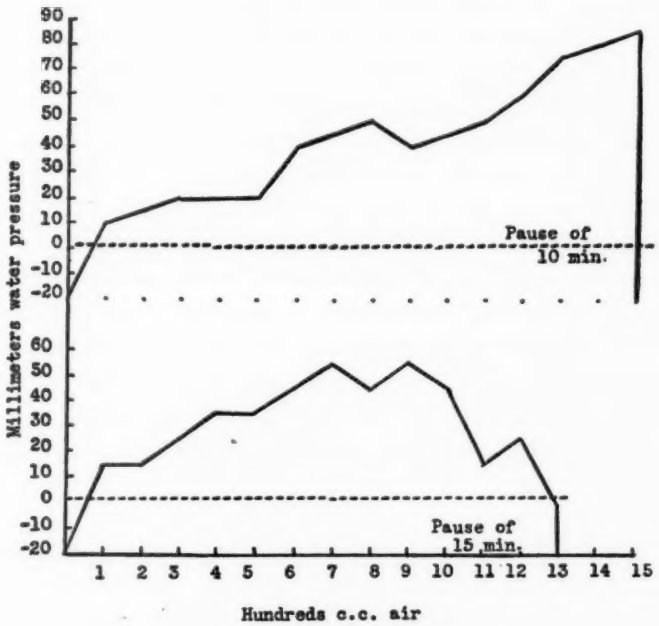

FIG. 9. TWO HUMAN CURVES

pneumoperitoneum are hybrid and depend upon the rate of inflation, mental state of the patient, the existence of any irritative effect of the

air on the peritoneal surface, the time elapsed between the inflation and the reading, volume of air given, and symptomatology. They readily conform, however, to the view of accommodation (see figures 7, 8 and 9). Any irritative effect of the air upon the peritoneum is usually manifested at the beginning of inflation by relatively high pressure-readings which drop to a lower level as inflation is continued. The presence of adhesions also results in early high pressures but associated with sharp pain and an increasing discomfort with inflation.

DISCUSSION

Abdominal accommodation may be regarded as a vital process, illustrating the "wisdom of the body." To maintain an intraäbdominal pressure close to that of atmospheric, both on addition or removal of content, there must be an intact neuromuscular system. Injury to either muscle or nerve impairs this function.

In the first few weeks of pregnancy in cats, Coombs noted that the pressure-curve rose much more slowly than in the normal state or in later weeks of pregnancy; one may infer the existence in early pregnancy of an already established accommodation to prepare for the growing uterus. Accommodation makes possible the presence of large abdominal tumors, with no derangement of visceral function except for sheer weight and pressure; for example, a small tumor near the common bile-duct produces obstruction but a large one in the pelvis does not affect the bile-duct because the abdominal pressure is not changed.

Such factors as posture, intraäbdominal fossae, and visceral displacement are of secondary and negligible importance in accommodation. The muscle contributes its elasticity and the nervous system makes possible the activity and changes in tone of the process. Combined, they produce an adaptability of the abdomen to adjust itself to any condition which may change its optimum pressure.

CONCLUSIONS

(1) There exists in the abdominal wall a process of adaptability to attempts to change intraäbdominal pressure. This process may be called "abdominal accommodation" and is of a high degree of efficiency.

(2) Abdominal accommodation is dependent upon an intact neuromuscular system, and may be regarded as a reflex mechanism in the conservation of body activity.

(3) This mechanism has a direct clinical bearing on intraperitoneal

procedures and the functional coördination of pleural and peritoneal cavities.

I wish to express my indebtedness to Doctors H. D. Chadwick and J. A. Kasper of Herman Kiefer Hospital and Doctor G. L. Leslie of Michigan State Sanatorium for their interest and aid which made this work possible.

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PULMONARY TUBERCULOSIS IN INFANCY, CHILDHOOD AND ADOLESCENCE[1,2]

J. P. NALBANT

Tuberculosis of the lungs in infants, children and adolescents has received much attention in recent years. There is much yet to learn but much has been done to clarify the subject by the recent plan of classification elaborated by the Committee on Diagnostic Standards of the National Tuberculosis Association. This classification divided pulmonary tuberculosis into childhood type and adult type. The childhood type is defined as the diffuse or circumscribed lesions in the lungs and associated tracheobronchial lymph nodes that result from a first infection of the pulmonary tissue with the tubercle bacillus. All subsequent infections are classified as adult-type lesions. A third group of cases in which the lungs are involved, but which do not, strictly speaking, belong in either of the above two is that group of acute generalized or miliary tuberculosis cases not infrequently seen in children. These should probably be classified as a complication of the two main groups, for in all cases there exists, undoubtedly, a lesion of either the childhood type or the adult type previous to a miliary spread.

It is not always easy to determine the dividing line between childhood-type and adult-type tuberculosis, but such a division is not entirely an arbitrary one as experimentally it is well shown that there is a marked difference in the response of the animal to first infection and to reinfection with the tubercle bacillus. The studies presented in this paper will indicate that the classification is usable and helpful in indicating the prognosis, and in so doing the course of treatment to be followed.

The present report is based on a study of 253 cases of pulmonary tuberculosis in children, of whom 120 had childhood type, 120 had adult type, and 13 had a generalized and miliary type of disease. Their ages ranged from 1 to 15 years. They all had definite parenchymal areas of infiltration demonstrated by the roentgenogram and were divided into the fol-

[1] From the Wm. H. Maybury Sanatorium, Northville, Michigan.

[2] Presented at a session of the Clinical Section at the thirtieth annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, May 15, 1934.

lowing three groups: (1) Childhood-Type Tuberculosis, (2) Adult-Type Tuberculosis, and (3) Miliary Tuberculosis. The last group was taken up separately to stress the fact that recovery may occur (see table 12), in spite of the belief that it is only a complication of the first two groups. Accordingly, the tables and their explanations will be discussed under separate headings except where comparison of the different types is made.

CHILDHOOD-TYPE PULMONARY TUBERCULOSIS

Table 1 shows a group of 120 children with childhood-type tuberculosis whose roentgenograms showed pulmonary consolidation with corresponding lymph-node enlargements near the root. The incidence of disease in this group was highest between the ages 4 and 11 years, next higher under 4 years, while only a few children had the disease between the ages 12 and 15. It is significant to note that one-fourth of the cases were found in infants, which stresses the fact that survey and examination of children of school-age is not entirely sufficient, that many infants with tuberculosis and the dangers of reinfection from the original source may be overlooked, if measures are not taken to examine all infants and young children of a household where an adult with tuberculosis has been discovered. The figures obtained for the two sexes, and the white and colored races show no particular difference. Apparently male and female and colored and white children alike are equally susceptible to the invading organism.

TABLE 1

Age-groups according to race and sex

AGE	WHITE	COLORED	MALE	FEMALE	TOTAL	PER CENT
Under 4 years	19	12	22	9	31	25.8
4–11 inclusive	44	42	45	41	86	71.6
12–15 inclusive	0	3	0	3	3	2.5
Total	63	57	67	53	120	100.0
Per cent	52.5	47.5	55.8	44.2	100	

The low incidence of childhood-type lesions in children between the ages 12 and 15 is not surprising at this time. However, as the anti-tuberculosis and preventive campaign spreads, and fewer infants and children are exposed to their tuberculous parents, then the number of adolescents who have not been infected with the tubercle bacillus will

increase, and when these uninfected adolescents later contract the disease they will have the childhood type of infection, thus causing an increase in the number of primary infections in adolescents and young adults, an infection which rarely needs any collapse therapy and whose prognosis is very good.

TABLE 2

Type of onset according to sex and color

TYPE OF ONSET	WHITE	COLORED	MALE	FEMALE	TOTAL	PER CENT
	per cent	*per cent*	*per cent*	*per cent*		
Sudden	27–42.8	31–54.3	31–46.3	27–50.9	58	48.3
Insidious	32–50.8	25–43.8	34–50.8	23–43.5	57	47.5
Unknown	4–6.4	1–1.9	2–2.9	3–5.6	5	4.2
Total	63–52.5	57–47.5	67–55.8	53–44.2	120	100.0

In table 2 the onset of the disease is classified in two groups; namely, (1) those children who gave a history of an acute illness which was diagnosed as pneumonia, influenza, bronchitis, whooping-cough, severe chest colds, etc., at or about the time of the onset of the present illness. These are classified under *sudden onset*, and comprise about 50 per cent of the children admitted to the Sanatorium with parenchymatous lesions. (2) Those children whose symptoms at the onset were vague, and consisted of loss of or failure to gain weight, listlessness, lack of appetite, undue fatigue, slight cough, occasional fever, gastric upsets, etc., or even no symptoms at all. This group was classified under *insidious onset*, and it comprised the remaining half of the children. There is no essential difference between the two sexes and the white and colored races so far as the type of onset of the disease is concerned.

TABLE 3

Exposure according to race

	EXPOSURE	NO EXPOSURE	TOTAL
	per cent	*per cent*	
White	55–87.3	8–12.7	63
Colored	44–77.2	13–22.8	57
Total	99–82.5	21–17.5	120

Table 3 is a comparison of the frequency of exposure in the white and the colored races. In so far as contact with an open case of pulmonary

tuberculosis is concerned, the number of those with such a definite history was somewhat greater among the white patients than among the colored. But the difference is insignificant and does not deserve further discussion. The noteworthy figures in this table are those in the columns of total exposures and nonexposures. From the above figures we may well conclude that exposure of the child to a tuberculous mother or father is the greatest factor in the incidence of this infection in infants and older children. Were it possible to hospitalize all persons who have active tuberculosis and positive sputum, a great step would be taken toward decreasing the number of victims to and eventual eradication of this family disease, by protecting the members of their families, especially those of school and preschool age.

TABLE 4

Physical signs, tuberculin reaction, positive sputum or faeces

	PHYSICAL SIGNS POSITIVE	PHYSICAL SIGNS NEGATIVE	TUBERCULIN		CULTURE OR GUINEA PIG INOCULATION FROM SPUTUM OR FAECES	
			Number tested	Number positive	Number examined	Number positive
Number of cases	86	34	115	115	53	24
Per cent	71.6	28.4	100	100	100	45.3

Table 4 gives a brief account of several points of interest. Physical signs of pathological significance were present in almost three-fourths of all cases. The tuberculin was positive in all who received the test. A most significant fact must be noted here; the discovery of the tubercle bacilli in the sputum or faeces of a number of these children; cultures and guinea-pig inoculations were done from the faeces and sputa of 53 children; in some cases the procedure was repeated. Twenty-four, or 45 per cent of this number, were positive for tubercle bacilli. Another interesting observation here may not be amiss. Not only in this group of definitely parenchymal disease have we been able to find the bacilli but also in a number of cases where very little if any demonstrable pathological process was seen in the X-ray. These interesting findings are some of the strongest arguments for hospitalization of tuberculous children whose lesions are still in the process of resolution.

TABLE 5

Location and distribution of lesion (includes all bilateral cases)

PART OF LUNG INVOLVED	UPPER 1/3	MIDDLE 1/3	LOWER 1/3	TOTAL	PER CENT
	per cent	*per cent*	*per cent*		
Right lung	25–33.4	32–42.6	18–24.1	75	58.5
Left lung	30–56.6	21–39.7	2–3.7	53	41.5
Total	55–42.9	53–41.4	20–15.7	128	100.0

Table 5 shows that approximately 60 per cent of lesions are found in the right lung and only 40 per cent in the left lung. Again, in the right lung lesions are most common in the middle third, less so in the upper third and least in the lower third. However, in the left lung consolidations are most common in the upper third, less in the middle third and peculiarly rare in the lower third.

The most noteworthy point in table 6 is the fact that although a great majority of children with childhood-type tuberculosis recover, there is a certain number that succumb to it or the complications resulting from it. Seven per cent of these children died of generalized tuberculosis or tuberculous meningitis.

TABLE 6

Course of disease according to treatment and presence of bacilli in sputum or faeces

	TOTAL NUMBER OF CASES	MEDICAL TREATMENT	SURGICAL TREATMENT	SPUTUM POSITIVE	SPUTUM NEGATIVE	PER CENT
		per cent	*per cent*	*per cent*	*per cent*	
Apparently arrested	99	95–96.0	4–4.0	21–21.2	78–78.8	82.5
Improved or quiescent	10	8–80	2–20	0	10–100	8.3
Stay too short to note change	3	3–100	0	0	3–100	2.5
Died	8	6–75	2–25	3–37.5	5–62.5	6.7
Total	120	112–93.3	8–6.7	24–20	96–80	100.0

The rôle of surgical collapse in the form of pneumothorax or phrenic-nerve surgery is debatable in childhood-type tuberculosis and is not required in the great majority of them, although it is definitely indicated in adult cases, as is shown below. However, the high incidence (50 per cent) of acute exacerbations of the disease in the positive-sputum group, and the higher incidence of deaths in the same group suggest that collapse therapy might be of value in such cases as these.

The course of the disease and its outcome are not influenced by racial

factors. This is well illustrated in table 7, the figures for apparently arrested, improved or quiescent cases being almost identical in the two races. The number of deaths among colored children was greater than among the white; however, the numbers are too small for fair comparison.

TABLE 7

Course of disease according to race

	APPARENTLY ARRESTED	IMPROVED QUIESCENT	STAY TOO SHORT	DIED	TOTAL
	per cent	*per cent*	*per cent*	*per cent*	
Colored	47–82.4	5–8.7	0	5–8.9	57
White	52–82.5	5–7.9	3–4.8	3–4.8	63
Total	99–82.5	10–8.3	3–2.5	8–6.7	120

Healing in the childhood type of tuberculosis takes place in three definite ways as determined by the roentgenogram. First, complete resolution of the consolidation leaving no trace of former disease in its wake; second, resorption of the lesion associated with formation of some fibrosis without calcification; third, complete calcification of the focus or foci

TABLE 8

Type of healing according to age

AGE	TOTAL NUMBER OF CASES	COMPLETE RESOLUTION	RESORPTION PLUS FIBROSIS WITHOUT CALCIFICATION	RESORPTION PLUS CALCIFICATION
		per cent	*per cent*	*per cent*
Under 4 years	27	7–25.9	3–11.2	17–62.9
4–11 years inclusive	79	27–34.2	26–32.9	26–32.9
12–15 years inclusive	3	0	3–100	0
Total	109	34–31.2	32–29.3	43–39.5

of infection. In table 9, 109 cases were grouped under the above three types of healing. Approximately one-third of all lesions showed complete resolution, one-third showed fibrosis without calcification, and one-third complete resorption plus calcification. Among children under 4 years of age, calcification occurred most frequently and fibrosis least frequently. In the group from 4 to 11 years of age, the three types of healing were in equal proportions. In the oldest group of children fibrosis was the prevailing form of healing. Racial characteristics appeared to modify

the type of healing. Table 10 indicates that calcification occurred more commonly in the colored group than in the white, and that complete resorption was the least common. In the white group the difference

TABLE 9

Type of healing according to race

	TOTAL	RESORPTION	FIBROSIS	CALCIFICATION
		per cent	*per cent*	*per cent*
Colored	52	12–23	16–30.8	24–46.2
White	57	22–38.6	16–30	19–31.4
Total	109	34–31.2	32–29.4	43–39.4

between the three types is not marked, although resorption was somewhat more common than fibrosis and calcification.

ADULT-TYPE TUBERCULOSIS

This type of tuberculosis in children and adolescents is the result of reinfection from an endogenous or exogenous source. It is the characteristic lesion of adolescence and no doubt very unstable and progressive if overlooked or untreated. The disease attacks mainly the apical regions from where it may spread downward; quite commonly an infraclavicular or basal lesion is an unexpected finding with a history of a

TABLE 10

Age—Race—Sex

AGE	WHITE	COLORED	MALE	FEMALE	TOTAL NUMBER OF CASES	PER CENT OF TOTAL
Under 4 years	0	2	2	0	2	1.6
4–11 years inclusive	22	12	21	13	34	28.3
12–15 years inclusive	65	19	7	77	84	70.1
Total	87	33	30	90	120	100.0
Per cent	72.5	27.5	25	75	100	

sudden onset. Table 10 shows the incidence of the disease in a group of 120 children up to the age of 15 inclusive. Only 1.6 per cent of this group were under 4 years of age, 28.3 per cent were between the ages of 4 and 11; 70 per cent were adolescents of from 12 to 15 years. The females predominated 3 to 1.

TABLE 11

Type of onset according to color and sex

	SUDDEN	INSIDIOUS	HAEMORRHAGIC	UNKNOWN	TOTAL
White	25	52	4	6	87
Colored	11	14	0	8	33
Total	36–30%	66–55%	4–3.3%	14–11.7%	120
Male	9	12	1	8	30
Female	27	54	3	6	90
Total	36–30%	66–55%	4–3.3%	14–11.7%	120

The onset of adult-type tuberculous disease is mainly of insidious nature. Only 30 per cent of these youngsters gave a history of an acute or sudden onset as compared to 50 per cent in childhood type. Those with no symptoms, or with only a vague history of fatigue, loss of weight, slight cough or failure to start the menstrual cycle, were 55 per cent, which is almost twice the number with sudden onset. The ones with a history of haemorrhage as the first indication of illness should, presumably, be included in the insidious onset group. The predominance of mild symptoms at the onset in the majority of cases is probably the main factor which prevents parents from suspecting their children of ill-health and which allows the disease to go on into its destructive stage, thus causing the large numbers of moderately and far-advanced disease with which the children are brought to the phyician. For this reason tuberculin testing followed by roentgenological examination of school children should be one of the major aims of all antituberculosis campaigns.

As soon as an adult-type lesion is diagnosed in a child or adolescent, it must be vigorously treated. It is one of the most treacherous forms of tuberculosis, and will rapidly go into far-advanced disease unless checked by immediate therapy. Approximately one-half of the figures shown in table 12 and table 13 indicate far-advanced disease on admission; not more than 18 per cent of the children came to us with minimal lesions. The far-advanced group furnished 72 per cent of deaths, the moderately advanced group 25 per cent, while the minimal group had only 2.5 per cent of deaths. As a contrast, of the total apparently arrested cases, 50 per cent were minimal and the rest were moderately advanced. No far-advanced case was discharged as apparently arrested. Thus it is apparent that those classified under the apparently arrested, quiescent

and improved group made up about half of the total, those unimproved or dead constituted the other half. When we consider the extent of disease with which these children came to us, cavities being present in 66 per cent, and positive sputum in 65 per cent of the total group, the results are not so discouraging, in so far as, of the total number, 49 per cent were apparently arrested or quiescent and 51 per cent unimproved or dead.

TABLE 12

Extent of disease and presence of cavity according to type of onset

TYPE OF ONSET	TOTAL NUMBER OF CASES	MINIMAL	MODERATELY ADVANCED	FAR-ADVANCED	CAVITY PRESENT	PER CENT OF CAVITY
Sudden	36	4	8	24	32	88.8
Insidious	66	17	31	18	36	54.5
Haemorrhagic	4	1	1	2	3	75.0
Unknown	14	0	7	7	9	64.2
Total	120	22	47	51	80	66.6
Per cent	100	18.3	39.1	42.6	66.6	

TABLE 13

Course of disease according to extent, presence of cavity and positive sputum

COURSE OF DISEASE	TOTAL NUMBER OF CASES	MINIMAL	MODERATELY ADVANCED	FAR-ADVANCED	PER CENT	CAVITY PRESENT	SPUTUM POSITIVE
		per cent	*per cent*	*per cent*		*per cent*	*per cent*
Apparently arrested	30	15–50	15–50	0–0	25.0	11–36.6	10–33.3
Quiescent	11	3–27.2	4–36.4	4–36.4	9.1	6–54.5	6–54.5
Improved	18	0–0	10–55.5	8–44.5	15.0	17–94.4	13–72.2
Unimproved	24	3–12.5	9–37.5	12–50	20.0	16–66.6	18–75
Dead	37	1–2.6	9–25	27–72.4	30.9	30–81	31–83.9
Total	120	22–18.3	47–39.1	51–42.6	100.0	80–66.6	78–65

Surgical treatment in the form of collapse therapy of adult-type pulmonary tuberculosis in childhood and adolescence is imperative. It is, so far, the only help that can be offered, and the results obtained justify the procedure. Bed-rest alone is not sufficient even if the disease is minimal in extent. This fact is well shown in table 14. Of the total of 120 children, 44.2 per cent received bed-rest alone as treatment and

55.8 per cent received collapse therapy in the form of pneumothorax or phrenic-nerve surgery. In the bed-rest group 30 per cent were apparently arrested, quiescent or improved, and 70 per cent died or were unimproved. On the other hand, in the group that received the benefits of active treatment, 64 per cent were apparently arrested, quiescent or improved and 36 per cent died. We may well conclude from the above figures, small as they are, that active treatment is not only justifiable, but necessary to cut down mortality in adolescent patients.

TABLE 14

Effect of treatment and extent of disease

TYPE OF TREATMENT	TOTAL NUMBER OF CASES	GROUP 1: APPARENTLY ARRESTED QUIESCENT IMPROVED	GROUP 2: UNIMPROVED OR DEAD	NUMBER OF FAR-ADVANCED CASES IN GROUP 1	NUMBER OF FAR-ADVANCED CASES IN GROUP 2	PER CENT OF TYPE OF TREATMENT
		per cent	*per cent*	*per cent*	*per cent*	
Bed-rest alone	53	16–30.0	37–70	8–50	33–89.1	44.2
Collapse treatment	67	43–64.1	24–35.9	33–76.7	24–100	55.8
Total	120	59–49.1	61–50.9	41–69.5	57–93.4	100.0

Table 15 shows the difference in mortality before the days of pneumothorax and phrenic-nerve surgery. Between 1922 and 1926, 87 per cent of adult-type tuberculosis cases in children admitted to the Wm. H. Maybury Sanatorium died. However, since 1926, with the advent of

TABLE 15

Comparison of results according to periods before and after surgical treatment was started in institution

YEAR	ADULT TYPE			CHILDHOOD TYPE		
	TOTAL NUMBER OF CASES	Apparently arrested or quiescent	Unimproved or dead	TOTAL NUMBER OF CASES	Apparently arrested or quiescent	Unimproved or dead
		per cent	*per cent*		*per cent*	*per cent*
1922–1926	23	3–13	20–87	8	5–62.5	3–37.5
1927–1933	97	56–57.7	41–42.3	112	107–95.5	5–4.5
Grand total 1922–1933	120	59–49.1	61–50.9	120	112–93.3	8–6.7

collapse therapy, only 42 per cent have died,—a very appreciable drop in the death-rate. These figures are undoubtedly modified somewhat by the

difference in extent of disease of the cases admitted between periods covered. The comparison between adult- and childhood-type lesions, so far as their prognosis is concerned, is well illustrated in the same table.

ACUTE GENERALIZED OR MILIARY TUBERCULOSIS

One of the most serious complications of tuberculosis in children, especially in infancy, is the haematogenous dissemination of tubercle bacilli into different parts of the body. It is, in the great majority of cases, a generalized tuberculosis which has heretofore been considered as invariably fatal. During recent years 13 cases of miliary tuberculosis have come under our observation. Of these, 3 fully recovered and 3 were markedly improved after a period of one year of hospitalization.

TABLE 16

Generalized miliary tuberculosis

RACE	TOTAL NUMBER OF CASES	APPARENTLY ARRESTED	IMPROVED	DEAD
	per cent	*per cent*	*per cent*	*per cent*
White	4–30.7	2–50	0	2–50
Colored	9–69.3	1–11.1	3–33.3	5–55.6
Total	13–100	3–23	3–23	7–54

Healing took place by calcification of the numerous foci of infection in one, and resorption in the others. It is evident from this that acute generalized miliary tuberculosis, in spite of its widespread distribution in the lungs and other organs, is not an entirely hopeless disease and a few children do recover. In three of the above group there were evidences of generalized tuberculosis. The clinical course of the disease was quite stormy in several of them for the first few months; however, the symptoms subsided within a few months.

Brief comment should be made as to the complications of tuberculous nature that presented themselves in this group of 253 children. The most common of these were, in the order of their incidence: pleurisy with effusion, suppurative cervical adenitis, chronic otitis media, phlyctenular conjunctivitis, pericarditis with effusion, Pick's disease and tuberculoma of the cerebellum. The majority of these complications were of transient nature and subsided promptly. A few were of necessity fatal.

SUMMARY AND DISCUSSION

The presentation of the above data reveals several very important facts. The most important of these is the fact that childhood-type tuberculosis is a definitely benign disease with a very good prognosis in contrast to the adult-type, which is progressive and destructive with good prognosis only in its minimal stage aided by adequate therapeutic measures. It is important to note that, in spite of the self-healing nature of the primary infection, from 6 to 7 per cent of our children so infected succumbed to the complications which arose during the course of their illness. These complications were mainly of tuberculous nature, among them the most common being pleurisy with effusion, pericarditis with effusion, generalized tuberculosis, tuberculous meningitis and finally remissions and acute exacerbations in or near the diseased area. The occurrence of these complications and the presence of tubercle bacilli in the faeces and sputa of a large number of these children seemed to justify the hospitalization of all those with active lesions.

Remissions or acute exacerbations occur not uncommonly during the course of childhood-type tuberculosis. This is corroborated by the fact that in 12 of our patients we observed the following interesting course of events. These children were admitted to the Sanatorium with undoubted childhood-type lesions characterized by roentgenological evidence of parenchymal disease which was accompanied by enlargement of the corresponding lymph nodes. Six of them had tubercle bacilli in the sputum. A few months later they showed fresh lesions in the previously infected lung that were very similar to the original lesion roentgenologically. The type of onset of the exacerbation was the same in all of them, and was characterized by fever, loss of appetite, general malaise and cough. All the symptoms lasted from two to four weeks. As soon as the fresh lesions were discovered, they were, by definition, classified as adult-type lesions and a few of them received surgical collapse, in view of the grave prognosis in adult-type lesions in children. Most of these children experienced retrogression and disappearance of their disease and are now discharged. It is interesting to note the fact that these secondary lesions or acute exacerbations, if we may call them such, were in every respect unlike adult-type lesions. The course and the outcome of these lesions were like the ordinary childhood-type case. After the acute symptoms had disappeared, the fever subsided, appetite returned and convalescence was rapid. The changes which occurred in the diseased areas of the lungs were exactly the same as those which had occurred

in the original primary infection, namely, resorption, fibrosis or calcification. None of the lesions showed evidence of a rapid, destructive process with consequent cavitation and generally downhill course that one would expect from adult-type tuberculosis in a child. It seems that it would be a mistake to classify these lesions with the adult-type group and subject them to surgical therapy, because it appears that these episodes in the course of childhood-type tuberculosis are acute exacerbations and are not adult-type tuberculosis. We are led to this conclusion by comparing the course and outcome of these lesions with those of true and definite adult-type disease which is all too malignant.

The reason these acute exacerbations behaved as primary infections probably rests in the fact that these children's bodies had not had sufficient time to lose their high allergy to the invading organism. Apparently it takes several years for this hypersensitivity to subside. When this hypersensitivity shall have subsided after a few years and the same children have become reinfected, then the response will be entirely different, and we shall have a more localized disease with less tendency to general reaction and greater destruction of tissue. Because of this great difference in prognosis, a sincere effort should be made to determine whether the child is suffering from a primary or childhood-type infection or an adult-type infection.

Adult-type tuberculosis in a child must not be allowed to go on indefinitely without institution of therapeutic measures. Time and again have we seen untreated minimal lesions go into moderately advanced or far-advanced disease in a short time, especially in the teen ages. The mortality can be reduced materially by treatment as shown in the above data. Also, the outlook for children with generalized miliary tuberculosis seems much more hopeful than heretofore considered.

CONCLUSIONS

1. A critical analysis of 253 cases of pulmonary tuberculosis of the childhood, adult and generalized miliary types is presented.

2. The transient nature of some secondary infiltrative lesions during convalescence from childhood-type tuberculosis is stressed.

3. The marked difference in the mortality rate between childhood-type and adult-type tuberculosis is presented.

4. The importance of early diagnosis and the effect of surgical treatment of adult-type lesions on the mortality rate is noted.

5. Considerable hope is extended to the child with miliary tuberculosis of the lungs or generalized tuberculosis.

THE PREPARATION OF SEIBERT'S TUBERCULIN-PROTEIN (*T.P.T.*) FOR DIAGNOSTIC PURPOSES[1, 2, 3]

LAWRENCE T. CLARK, ARTHUR D. EMMETT AND ORSON D. BIRD

The object of the present paper is to report upon the practical development of Seibert's (1) tuberculin protein, purified by trichloracetic-acid precipitation, and designated by her as *T.P.T.* In particular, we wish to stress the distinct advantage of this product for diagnostic purposes. Quoting from Seibert and Munday (1) on this point: "Preliminary clinical tests of the *T.P.T.* indicate that 0.000,1 mgm. or less will produce a skin reaction in tuberculosis patients, and that it is a safe and satisfactory product for diagnostic purposes."

However, this highly potent dry *T.P.T.* in its original powder form is impractical for use as a diagnostic agent, since it is insoluble in saline solution. It must first be dissolved in dilute alkali, and then carefully neutralized with acid. Further, it would be necessary to weigh out as minute a quantity as 0.1 mgm. to prepare a dilution suitable for intracutaneous injection. Even this small amount would provide 10 cc. of solution, which is enough for 100 doses. It is obvious that the stability of such a dilute solution would be questionable. Aside from this, it is evident that it is undesirable, as well as impracticable, to dispense such a

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[2] In coöperation with the Research Committee of the National Tuberculosis Association.

[3] The tuberculin protein, *T.P.T.*, described in this and the two following papers is essentially the same as the tuberculin-protein described in the literature as M.A. 100. They were both developed as the result of the work of Dr. Florence B. Seibert in coöperation with the Medical Research Committee of the National Tuberculosis Association and the various members of coöperating groups. *T.P.T.* Seibert is prepared by ultrafiltration and trichloracetic-acid precipitation; M.A. 100 by salting-out and alcohol precipitation. The two manufacturing houses preparing them followed the recommendations of Dr. Seibert in that work. The diagnostic results of the tuberculin protein prepared by the two methods has been the same.

In recent months the group has been working in coöperation with the United States Department of Agriculture for the development of a standard tuberculin which is essentially the same as *T.P.T.* and M.A. 100 and which, it is hoped, will be used uniformly in the United States. It will have the advantage of being referable to the Government standard tuberculin. Publications on this later coöperative project will appear from time to time.

highly potent dry powder, for the clinician has neither the time nor equipment for handling such material. We feel, therefore, that the ideal condition calls for preparing the *T.P.T.* in a soluble form and in turn combining this with definite amounts of an inert soluble dry diluent. Such a mixture would be immediately soluble for use; would be in dry-powder form, and therefore stable; and further, convenient in amount and have sufficient bulk to permit of ease of handling.

HISTORICAL

A brief review of the sequence of the essential points followed by Seibert and associates in their project may be of assistance.

They used Long's (2) synthetic nonprotein medium and studied the metabolic end-products formed during incubation of the culture. The tuberculin culture-filtrate, containing only pure chemicals in addition to the products elaborated by the tubercle bacillus, was naturally the fertile field for isolation and study of these end-products. This work developed progressively according to the following phases:

1: Salting out from the culture-filtrate the active protein with ammonium sulphate.
2: Concentration and purification of the culture-filtrate by dialyzing through collodion membrane, this process being designated *ultrafiltration.*
3: Preparation of a dry tuberculin-powder by precipitating the protein with ammonium sulphate at the isoelectric point from the material concentrated by ultrafiltration.
4: Preparation of a dry tuberculin-powder by precipitation of the specific protein with trichloracetic acid from the material concentrated by ultrafiltration.

Comparing the ultrafiltration procedure with the precipitation of the protein from the culture-filtrate by salting out, we found the former superior to the latter, in that very little denaturing took place and that it gave a tuberculin which was about 10 times more potent per unit of whole protein. In the precipitation of the protein, either by ammonium sulphate at the isoelectric point or by trichloracetic acid, from the purified and concentrated fraction left on ultrafiltration of the culture-filtrate, a still more highly purified tuberculin was obtained. Both of these procedures gave a powder which was undenatured, carried less of the carbohydrate, and could be easily duplicated. The latter of these two methods, namely, precipitation with trichloracetic acid, was deemed the more

desirable, since it was easier and less time-consuming. The tuberculin powder produced by this method was designated *T.P.T.* It was an insoluble protein which could be put into solution by the addition of a weak alkali, then neutralized with dilute hydrochloric acid and diluted to the required concentration.

EXPERIMENTAL

In these laboratories we first directed our efforts along this line in 1928 when we coöperated with the Research Committee of the National Tuberculosis Association, in supplying material in quantity for chemical study of the tubercle bacillus and its by-products. Beginning first with the acid-fast timothy bacillus (3), several steps in connection with the growth of the culture, filtering off the bacteria, and separation of the filtrate were developed. Later, we took up the question of concentration and purification of the filtrates from the growths of the human, bovine and avian tubercle bacilli.

In this, we followed closely the work of Seibert and her associates (1), and modified their method only as the need for increased production developed, rigidly maintaining, however, her fundamental principle intact. The filtrate, after the incubation of the respective organisms on Long's medium, was ultrafiltered, and finally the residue, called by some *ultraprotein*, was treated with trichloracetic acid to throw out the specific protein *T.P.T.*

Growth of Cultures and Filtration: The cultures of the tubercle bacilli used in each case were: For human, Saranac Lake strain H37; for bovine, strain 523; and for avian, strain 531. We ascertained that the nature and rate of growth of the organisms were definitely dependent upon a reasonably close adjustment of the pH of the sterile medium. Thus, if the reaction was too acid, growth was slow and scanty, even after several weeks' incubation beyond the usual time.

The respective cultures were planted in special one-litre cylindrical pyrex-glass bottles with small necks. In each, there was 200 cc. of Long's medium, prepared from chemically-tested reagents. After carefully seeding, by floating off a loop of the culture on to the surface of the medium, we placed the flasks on their sides and incubated them for 6 to 8 weeks at 37°C. As many as from 1,500 to 2,000 such bottles were started at one time. In harvesting, we rejected those cultures in which the mat or veil of bacilli covered approximately less than two-thirds of the surface of the medium. The separation of the tuberculin-filtrate

was done by filtering off the bacteria aseptically and quickly, with slight suction, on a large, well-glazed Buchner funnel which had very small holes. Even though no filter-pad or cloth was used, the filtrate was remarkably free from visible clumps of bacteria. The filtrate was next rendered sterile by first adding phenol to 0.5 per cent, allowing the mix-

TABLE 1

Production of culture-filtrate

EXPERIMENT	CULTURE MEDIUM NUMBER	INCUBATION TIME (WEEKS)	CULTURES PLANTED	CULTURES HARVESTED	YIELD OF FILTRATE (LITRES)	REDUCTION IN VOLUME PERCENTAGE	DATE INCUBATED
Tubercle bacillus (human H37)							
H-1	094201a	6	677	623	96	23	August, 1929
H-2	094201b	6	432	426	64	25	September, 1929
H-3	094273	6	1050	1024	126*	—	November, 1929
H-4	094942	9	190	180	26	28	July, 1931
Total			2349	2253	312	24	
Tubercle bacillus (bovine 523)							
B-1	094092	8	1949	1892	284	25	May, 1929
B-2	094306	6	1043	1034	161	22	January, 1930
Total			2992	2926	445	24	
Tubercle bacillus (avian 531)							
A-1	094148	8	476	458	58.3	36	July, 1929
A-2	094362	6	1033	991	144.0	27	December, 1929
Total			1509	1449	202.3	30	
Timothy bacillus 1589							
T-1	094129	4	957	951	153	20	July, 1929

* Part of filtrate lost.

ture to stand for 24 hours at room temperature, and finally passing it through a Mandler filter. The filtrate was tested for sterility and then stored in the refrigerator to be held until it could be handled for ultrafiltration and concentration.

In table 1 are presented the data showing the various bacilli-cultures used, giving, in each case, the time of incubation; the number of cultures planted and recovered; the yield of culture-filtrate in litres; and the percentage reduction in volume or concentration due to evaporation.

Ultrafiltration: In the procedure for ultrafiltration of the sterile culture-filtrates, we used large alundum thimbles, designated *R.A. 36*, and measuring 1.75 x 7.5 inches. They were arranged in batteries of 9 each, being connected in series to a common outlet. Each battery of tubes was set in a rectangular glass aquarium-jar, which had an approximate capacity of 8 litres. Several of these set-ups were made and in turn connected in series.

The thimbles were coated with collodion, by dipping them in a solution of gun-cotton and glacial-acetic acid (11 gm. in 100 cc.), and cautiously

TABLE 2

Ultrafiltered culture-filtrate (ultraprotein)

ULTRAPROTEIN NUMBER	CULTURE FILTRATE USED	FIRST CONCENTRATE	WASH WATER	FINAL CONCENTRATE	CONCENTRATION FACTOR
		Tubercle bacillus (human H37)			
	cc.	*cc.*	*cc.*	*cc.*	
094250	95,500	800*	38,000	835	114
094298	34,000	600	10,000	515	66
094317	30,100	400	12,000	440	68
094417	72,100	2000	34,000	2200	33
094978	11,000	300*	5,500	318	35
		Tubercle bacillus (bovine 523)			
094209	284,000	3800	40,000	3940	70
094579	54,000	1000	25,000	1090	50
		Tubercle bacillus (avian 531)			
094367	58,300	1500	15,000	1090	54
		Timothy bacillus 1589			
094279	30,400	350	18,000	195	155

* Approximate.

rotating until a uniform film was formed. Several concentrations of the gun-cotton were tried, but the 11 per cent solution proved to be the most efficient in our hands, in that it held back the tuberculin-protein very well, as shown by the negative flocculation tests when trichloracetic acid was added to some of the ultrafiltrate. At the same time, this membrane was porous enough to permit of a filtration rate which was practical on a large scale. The coated thimbles were then placed in distilled water and washed by ultrafiltration until all the excess acid was removed.

In table 2 we present data showing the details as to volume of culture

filtrate used; volume of concentrate before and after washing; and the degree of concentration for the different bacterial cultures. The protein content in each case was determined at the time by the centrifuge trichloracetic-acid method of Seibert (1). Later it was found that this procedure gave inaccurate results; so these data are omitted.

The first four ultraprotein solutions in table 2, nos. 094250, 094298, 094317, 094417, were combined to make composite number 094873. This mixture was found to have the following ultimate analysis:

	Mgm. per cc.
Total solids	34.4
Total nitrogen	2.28
Protein nitrogen	1.15
Nonprotein nitrogen	1.13
Protein (N. x 6.25)	7.19
Peptones, etc. (N. x 3.12)	3.52
Non-nitrogenous (by difference)	23.69

Preparation of T.P.T. (Human): Aliquot portions of the above ultraprotein 094873 were taken for preparing Seibert's *T.P.T.* Our procedure was essentially as follows: To 500 cc. we added, while cautiously stirring, an equal volume of 50 per cent trichloracetic acid (250 gm. of acid made up to 500 cc. with water). This gave a 25 per cent acid-protein mixture. It was allowed to stand overnight, when the bulk of the supernatant part was decanted and the protein then centrifugated. After washing the precipitate with trichloracetic acid several times, the separated protein was then thoroughly washed with ether to remove the trichloracetic acid and traces of water. This gave the powdered tuberculin *T.P.T.*

Tablets of T.P.T. for Diagnostic Use: In order to bring this dry powdered tuberculin into a convenient form for clinical use, it was treated with alkali to render it soluble, and then combined with increasing amounts of lactose to produce sterile tablets of convenient size and *T.P.T.* content. The amount of lactose added in each case was calculated so as to give concentrations of the *T.P.T.* powder in each 30 mgm. tablet equal to 0.001, 0.01 and 0.1 mgm. respectively. Dissolving these tablets in 1 cc. of diluent gives dilutions of 1:1,000,000, 1:100,000 and 1:10,000, respectively, of the *T.P.T.* From these dilutions 0.1-cc. amounts may be injected intracutaneously according to the following:

1st dose, 0.1 cc. = 0.0001 mgm. *T.P.T.*
2nd dose, 0.1 cc. = 0.001 mgm. *T.P.T.*
3rd dose, 0.1 cc. = 0.01 mgm. *T.P.T.*

Further, to make this procedure still more practicable for the clinician, single *T.P.T.* tablets of each strength may be placed in empty 1-cc. sterile rubber-capped bulbs. When ready for use, 1 cc. of the diluent is admitted aseptically into one of these bulbs containing the *T.P.T.* tablet of desired strength. The tablet quickly dissolves, and the 0.1-cc. doses for intracutaneous dilution are taken from this bulb.

The authors are indebted to Dr. H. S. Willis of the Detroit Municipal Sanatorium, Dr. J. B. Barnwell of the University of Michigan and Dr. O. M. Gruhzit of this laboratory, for their coöperation in proving the practicability of incorporating serial dilutions of tuberculin powder in sterile tablet-triturates for convenience in arriving at dilutions for making diagnostic tests.

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A NOTE ON COMPARATIVE TESTING WITH SEIBERT'S TUBERCULIN-PROTEIN (*T.P.T.*)

JOHN M. APPEL, BRUCE H. DOUGLAS, TECKLA ROSENBUSCH AND HENRY STUART WILLIS

During the past two years an extensive study has been conducted on tuberculin sensitiveness in tuberculous patients. This study has aimed to ascertain whether sensitiveness is constant or whether it fluctuates: and, if the latter is true, whether fluctuations can be correlated with significant clinical changes or trends in the course of the disease. It has sought to demonstrate whether possible correlations of this sort might have prognostic significance. In the course of this work (of which this is a brief, preliminary statement) recourse has been had to the use of several different kinds of tuberculin, which were observed from the standpoints of their reliability, potency, comparability and, to some extent, antigenicity.

The products used were the following:

1: Old Tuberculin, some of which was obtained on the market and some prepared in our laboratory.
2: Ultrafiltrate: Prepared by filtration and dialysis. Seibert (1) first made this product and has described it, both as to content and manner of production. Briefly, it consists of the active, specific principle that has been separated by filtration and dialysis from the other ingredients of media on which tubercle bacilli have grown. It is an almost chemically pure product. It elicits a tuberculin reaction in infected man and animal, and is of protein nature.
3: Trichloracetic Precipitate Tuberculin: This product is called *T.P.T.*, and is described by Seibert and Munday (2) and by Clark, *et al.* (3). It is prepared by precipitating the partially dialyzed tuberculin just described. The precipitated material is dry and is accurately measurable.
4: T.P.T. Tablets: This is simply a convenient form of the precipitate and has been described by Clark, *et al.* (3).

Altogether, somewhat over 1200 patients were tested, many of them repeatedly over a period of more than a year. Weak dilutions were used first, and the dilutions were increased in strength in those failing to respond, until reaction was elicited. At times the type of tuberculin was changed or compared with another type. When this was done, compari-

son was made on a group of from 40 to 50 patients, who would be tested with the dose which last produced a reaction, together with another tuberculin in two or three different dilutions.[1] In this manner the several tuberculins enumerated were checked against each other.

The first one used was Seibert's ultrafiltrate. Tests were made on certain patients every three weeks, and on others every two and one-half to three months, and were carried on at these intervals for nearly a year. At this time approximately 50 of the patients who were tested with ultrafiltrate were tested also with the newer *T.P.T.*, in a range of dosage sufficient to indicate the relative strength of the two products. It turned out that the reactions in general were slightly greater in extent with the latter product, but it was rare to find a reaction to one in a person who failed to react to the other.

The study was carried on from this point for over six months with *T.P.T.*, when this product was similarly compared with *T.P.T.* in tablet form. In 83 patients the latter corresponded essentially to the *T.P.T.* that was prepared in solution, and routine testing was continued with the tablets. They were found to be a satisfactory source of tuberculin.

On several occasions Old Tuberculin in varying dilutions was used on patients at the time of the test with each of the three products described, in order to compare a new tuberculin with one that is established and widely used. It is difficult to compare two such products when the unit of measure is not the same, and no exhaustive effort was exerted to make exact comparisons. Rather, it was sought to determine how the new product would stand in its average initial dose when compared with the conventional dose of 0.1 cc. of 0.000,1 O. T. In one group of 50, O. T. gave a slightly more intense reaction in twelve, a slightly less intense reaction in ten, and approximately the same degree of reaction in twenty-eight, as compared to *T.P.T.* But in no case was there a reaction to O. T. and not to *T.P.T.*, and the reverse was also true. The variations noted were usually not greater than 5 mm. in diameter of zone of redness or a slightly greater degree of induration. This question has been presented in detail by Barnwell and Pollard (4).

It was routine to begin with a small dose, because we were dealing with

[1] Objections have been raised to this procedure on the ground that the ordinary reaction may not be a purely local affair and that thus more than one injection done at the same time may influence the intensity of each. This point has not been studied sufficiently, but previous experience inclines us to the opinion that such procedure has no effect upon the reaction to any of the concurrent injections.

a group of people of whom many were clinically ill. The initial dose was 0.1 cc. of 0.000,01 mgm. of tuberculin and this was followed three or four days later with stronger doses in the nonreactors. The results were roughly as follows:

Reaction to 0.1 cc. of dilution	*Percentage of additional patients reacting*	*Percentage of all patients reacting*
0.000,01 mgm.....		20+
0.000,1 mgm.....	44+	64+
0.001 to 0.1 mgm.....	34+	98+
0.01 to 0.1 mgm.....		98+
Failure to react to 0.1 mgm....		2−

The question of deterioration with age obviously arises. In order to obtain data upon this point, one lot of tablets was kept for 10 months at room temperature and a comparable lot was kept in the ice-box at 4°C. for the same period. These were then put in solution and applied to the skin of 52 patients, along with a freshly prepared solution of *T.P.T.* The reactions to the dose employed for the test (0.1 cc. of 0.000,1 mgm.) were vigorous and varied but little in intensity. In two patients there was a failure to react (the patients had redness but no induration) to the product kept on ice. In all others reaction was conspicuous and clear-cut to all three specimens.

As a result of these observations, we have come to use *T.P.T.* in much of our work. The advantages are (1) the product is exactly measurable, which marks a very genuine advantage because comparable doses may be duplicated at will; (2) the potency is high and constant; (3) the active principle remains unimpaired in the dry state for at least 10 months at room temperature; (4) the convenience of using the tablets in desired dilutions is noticeable; and (5) the solution remaining after the average test may be discarded and thus the question of loss in strength of weaker dilutions may be readily obviated.

Another advantage put forth for a chemically purified tuberculin over Old Tuberculin is that the purified product contains one more or less analyzable substance and is without any ingredients of media, which include other protein products, glycerine, sodium chloride, etc., in varying proportions. The use of tuberculins which contain the ingredients of media introduces unknown and potentially complicating factors, which employment of purified products clearly does away with.[2]

[2] This is certainly sound reasoning theoretically. However, all who have used Old Tuberculin very extensively will attest that it has long been a standby of reliability and constancy. The inability to accurately measure Old Tuberculin is the chief reason for giving it second place.

The purpose of this brief paper is to describe the observations in so far as response to the different types of tuberculin is concerned. A more detailed consideration of the work will be published later.

The products used were kindly furnished by Parke, Davis & Company.

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A COMPARISON OF OLD TUBERCULIN WITH TUBERCULIN PROTEIN T.P.T.[1, 2]

JOHN B. BARNWELL AND H. M. POLLARD

If skin sensitiveness to tuberculin in persons infected with tubercle bacilli fluctuates within large limits, any study of these fluctuations, any attempt to detect all those infected, and any attempt to discover among the uninfected the onset of sensitiveness or infection, demands a stable tuberculin and an accurately measurable one. That tuberculin sensitiveness does fluctuate widely is amply demonstrated. The lapse of months or years between infection and disease, and the passage of even more years before a considerable number of controlled instances of infection and disease can be collected for study, emphasize the absolute requirement of a test-dose that can be accurately measured, and as accurately repeated years later.

This report concerns a study directed toward the selection of such a tuberculin, to be used in the larger study now under way. At the time this study was begun (November, 1931) Seibert's T.P.U. (1) seemed to meet these requirements better than any tuberculin then available, and was used until September, 1932. Work with T.P.U. was then abandoned, not because of any dissatisfaction with the results, but because Seibert's more recent T.P.T. (2) (Clark, *et al.* (3)) had become available to us. T.P.U. was replaced by T.P.T. in all of our work because of the theoretical advantages of T.P.T. over T.P.U. chemically, the greater stability of the dry protein form, and the practical convenience of the tablet form (Willis (4)).

MATERIALS AND METHODS

Since O.T. has been used widely for so many years in tuberculin surveys, and since most workers are familiar with it, we have employed it as a control in all of the foregoing tests; in each case giving the protein in

[1] From the Department of Internal Medicine of the Medical School and the University Hospital, University of Michigan, Ann Arbor, Michigan.

[2] T.P.T. is a protein obtained from the unheated culture filtrate from tubercle bacilli grown on synthetic medium. The designation T.P.T. was given by Seibert (2).

the right arm and the O.T. in the left arm intracutaneously. One lot of O.T. used was kindly furnished us by Aronson and standardized (Lot A378.3) by him at the Phipps Institute, Philadelphia (5). The use of this tuberculin is reported in this paper in the dilutions of 1–50,000, 1–10,000 and 1–100 on students of group 1 only (table no. 3, chart 1). From then on we adopted a second Old Tuberculin. This was done merely to assure ourselves of an ample supply of the same stock lot over a prolonged period.

This lot (P.D. Rx. 06559) was prepared in October, 1929, and has been kept continuously at a temperature of 2° to 5°C. Kjeldahl determinations on a specimen of this lot yielded 11.50 mgm./cc. total nitrogen, of which 1.00 mgm./cc. or 8.7 per cent of the total nitrogen was protein nitrogen, the balance being nonprotein nitrogen. With the exception noted above, all O.T. controls reported here were made with this second lot.[3]

The T.P.T. was received in both solutions (1.0 & 10.0 mgm./cc.) and dry-tablet form. From these stock solutions appropriate dilutions were freshly made every three days, with quantitative chemical technique, preserving bacteriological sterility, and kept in the refrigerator. The dry T.P.T. tablets were received in vials of three strengths, 0.001, 0.01, and 0.1 mgm. per tablet or vial. The night before, or the day of use, the tablets were dissolved in 1.0 cc. of sterile physiological salt solution without preservative or buffer. This saline has a pH of 6.7 to 6.9 and was the diluent in all of our work. An ordinary tuberculin syringe and needle were used to inject the 1 cc. into the rubber-capped vial. By weighing the vials before and after, the average error was found to be 1.3 per cent. The vials were shaken until the solution was clear to the naked eye which usually required only a few minutes.

We doubted the possibility of such pharmaceutical accuracy as could place exactly 0.001 mgm. dry protein in each tablet. To test the evenness of the distribution of the protein among the tablets, we numbered each vial and recorded it with each test. As each test was controlled with the simultaneous administration of O.T. we had a means of detecting either absence of protein or conspicuous variation in amount of protein. In every instance in which all the tests from a single vial were negative, so also were all the controls. Contrariwise no vial yielded all positives when all the controls were negative. This was true of the 167 vials of all three strengths with which this check was made. As the

[3] This Old Tuberculin, as well as Seibert's T.P.T. and P.P.D., was made available to us through the courtesy of Parke, Davis & Company.

vials usually will supply only 6 or 7 tests, it may be mere coincidence that no such discrepancy occurred, but there is this evidence of the apparent uniformity of these tablets in protein content. Furthermore, in increasing the dose on nonreactors, each successive increase found a consistent percentage of positives (tables 3, 4 & 5) and no unexpectedly large reaction was encountered. The reaction was never out of proportion to the control O.T. The percentage of mild and severe reactions was markedly constant in the three strengths used, and comparable to the O.T. as shown in table 1. These facts we regard as additional evidence of the constancy of protein content in the tablets.

Every precaution was taken to maintain the quantitative accuracy of the intracutaneous deposition of the test dose. The diameters of the

TABLE 1

Comparison of intensity of reaction between O.T. and T.P.T. in percentage of reactors

INTENSITY OF REACTION	O.T.						T.P.T.			
	Dilution					Total percentage	Mgm.			Total percentage
	1–100,000	1–50,000	1–10,000	1–1000	1–100		0.0001	0.001	0.01	
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
+	90	87	69.5	34.9	65.0	62.8	70.0	42.6	60.0	59.4
++	10	7	24.2	19.7	20.6	21.2	12.2	21.6	25.1	19.4
+++	0	7	5.4	44.0	14.3	15.6	17.1	26.8	14.8	21.1
++++	0	0	0.7	1.5	0	0.66	0.44	0	0	0.075
Total number..	10	15	147	66	63	301	228	227	135	570

erythema and oedema were recorded in millimetres at 24, 48 and 72 hours. It was noted as positive if there was at 24 or 48 hours an oedema or induration of at least 5 x 5 mm., with persistence of the oedema or induration for an additional 24 hours, regardless of the amount of erythema. For tabulating the intensity of the reaction the one-, two-, three- and four-plus criteria of Aronson (10) were used. If at 48 hours either tuberculin was negative, the next stronger dilution was given into that arm. This procedure was repeated for three dilutions of each material so that the nonreactors received injections on the first, third, and fifth days, and a total of six injections.

DOSAGE

Every test dose of every tuberculin was contained in 0.1 cc. The O.T. dosages are reported in the customary terms of dilution of the

stock or crude O.T. We have chosen to report T.P.T. dosage as the actual amount of protein in mgm. contained in the 0.1 cc. of solution received into the skin. It is impracticable to report O.T. so, because of the variation in protein content, and nonspecificity of much of the protein.

For convenience our three "comparable" dilutions of O.T. and T.P.T. are given here in terms of both systems.

	Dilution	*Weight of tuberculin per dose mgm.*	*Weight of protein per dose mgm.*
First dilution			
O.T.	1–10,000	0.01	0.000,062,5
T.P.T.	1–1,000,000	0.000,1	0.000,094
Second dilution			
O.T.	1–1000	0.1	0.000,625
T.P.T.	1–100,000	0.001	0.000,94
Third dilution			
O.T.	1–100	1.0	0.006,25
T.P.T.	1–10,000	0.01	0.009,4

Under "Dilution" the ratio given for O.T. is actual and accurate; that for T.P.T. is on the assumption that 0.1 mgm. of dry protein dissolved in 1.0 cc. of salt solution is a dilution of 1/10,000. Under "Weight of tuberculin per dose," the figures given for O.T. are based on the commonly used assumption that 1.0 cc. of O.T. contains 1,000 mgm. of tuberculin; for T.P.T. the weights are actual, and as accurate as 1/10th of the weight of the dissolved tablet, as labelled by the manufacturer. Under "Weight of protein per dose" the figures for O.T. are derived from the protein nitrogen multiplied by the factor 6.25; for T.P.T. the figures represent the approximate average protein content of the T.P.T. lots supplied us, there being anywhere from 2 to 8 per cent carbohydrate remaining in the T.P.T. The importance of these figures lies in the relative amount of protein in the doses compared. In these three dilutions the O.T. contained an average of only 0.665 of the protein in the T.P.T. Conversely the T.P.T. contained 1.50 more protein than the O.T. in the "comparable" dosages as we used them. This ratio will be referred to in the discussion of the results.

The dosage of T.P.T. which we adopted had previously been determined by Clark on animals, and by Willis in a large experience with patients, and in addition by Chadwick and Derby at the Herman Kiefer Hospital in Detroit.

THE X-RAY CONTROL

X-ray examination was ordered on all tuberculin reactors, whether to the O.T. or tuberculin protein, and on as many nonreactors as possible. A single posteroanterior film (not paper) was sufficient, if negative beyond all doubt. In all cases of uncertainty this was followed by a posteroanterior stereoscopic pair, and often by laterals or obliques or such other special technique as the problem suggested. Many of the individuals reported on have had serial X-ray studies over a period of months or even years. The evidence from the entire series is considered in each case, choosing, however, the status in the film nearest the reported tuberculin.

The interpretations of the X-rays were made and recorded by three individuals separately, who had no knowledge of the tuberculin reaction. These individuals were Dr. Carleton B. Peirce, Associate Professor of Roentgenology, and the two authors. All variations from the strict normal were recorded, but for the purposes of this study an effort was made to make a sharp distinction between "positive" and "negative" findings. The "positive X-rays" are those containing any evidence whatever of undoubted tuberculous infection, past or present. The "negative X-rays" are those containing no such evidence. Before an individual's record was marked "positive X-ray" we required substantial agreement among the three observers.

Our criteria for a "positive X-ray" were any of the following:

(1) Ghon's tubercle.
(2) Calcium deposits within the parenchyma, but scattered and more irregular in outline than a typical Ghon's tubercle.
(3) Calcified lymph nodes at the root.
(4) Definite "tuberculous infiltration" within the upper third of the parenchyma.

As these criteria were constructed for controls on our tuberculin results, and not for purposes of therapy, such aetiologically indefinite evidence as "hilar infiltration," "hilar lymph nodes" (not calcified) and all pleural involvements were recorded as "negative."

Dr. Peirce has been kind enough to submit his criteria which follow:

As criteria for the roentgen diagnosis of previous tuberculous infection in the adolescent period, we consider calcium deposition in the tracheobronchial lymph nodes, the pleura, or in a parenchymatous scar as positive evidence.

Focal fibrosis in the peripheral parenchyma, especially in the upper lung fields, with or without tracheobronchial adenopathy, is considered presumptive evidence. Similarly, hilar adenopathy without calcium deposit is presumptive evidence in the absence of signs of leukaemia or lymphoblastoma. The focal parenchymatous infiltration of active pulmonary tuberculosis needs no elucidation.

In further consideration of calcium deposition, the so-called tubercle of Ghon is the only lesion presenting relatively homogeneous consistency. All others will present a somewhat irregular, flocculent character, persistent in all projections, whereas blood-vessels in optical section will not persist in two or more views. The uncommon occurrence of calcareous glands following infestation with ascaris removes this on the basis of probability.

Focal fibrotic areas in the parenchyma are so rarely the residuum of a nonspecific lesion that they, too, are considered highly presumptive. These, further, are usually accompanied by hilar changes or peritruncal fibrosis leading directly to the hilum.

Hilar adenopathy in the adolescent is most commonly of tuberculous origin. It has been seen in undulant fever, pertussis and streptococcic pneumonia, as well as in the leukaemias and lymphoblastomata. However, these others so rarely occur without distinguishing clinical signs or history as to offer little confusion. Regression within three to six weeks after therapeutic test of roentgen irradiation will ordinarily eliminate the nontuberculous adenopathies.

Apical pleuritis, nonaxillary pleuritis and pleurophrenic adhesions as well as noncalcareous beading along the bronchovascular trunks, or undue prominence of these truncal shadows will warrant further observation of the patient. We do not consider them *prima facie* evidence of previous tuberculous involvement.

For the purposes of this study Dr. Peirce's report was recorded as "positive" only when he mentioned his "positive evidence" detailed above. His "presumptive evidence" was recorded as "negative." Throughout the tables and discussions that follow the words "positive X-rays" and "negative X-rays" will be used only in the sense that is defined in this section.

RESULTS

An analysis of reactors in the various age groups for both O.T. and T.P.T. is shown in table 2. It is of significance here that in each age group T.P.T. gave a consistantly higher percentage of reactors.

The subjects tested are divided into three groups. Group 1 consists of 298 first-year college women tested in September, 1932. This group received either 1–100,000 (P.D.) or 1–50,000 (Aronson) as the first dilu-

tion of O.T., 1–10,000 and 1–100 (Aronson) as the second and third dilutions. T.P.T. was used throughout in three dilutions only, 0.0001 mgm., 0.001 mgm., and 0.01 mgm. per dose.

Table 3 gives the results of the first series of simultaneous tests with T.P.T. and O.T. on the college women. Lines A and B show the result of the first or weakest (0.0001 mgm.) T.P.T. and the two dilutions of O.T. used to control it. Five times as many reacted to T.P.T. 0.001 mgm. as to O.T. 1/100,000 dilution. This is in no way surprising as there was 15 times as much total protein in the T.P.T. dosage. When the same T.P.T. dosage is compared with O.T. 1/50,000, with only 1/7th the total protein of the T.P.T., only 1.2 times more reacted to the T.P.T. When

TABLE 2

O.T. age incidence, high-school students and college women

AGE	NUMBER IN SERIES	1–10,000			1–1000				1–100			
		Number tested	Positive	Per cent positive	Number tested	Positive	Per cent positive	Adjusted per cent positive	Number tested	Positive	Per cent positive	Adjusted per cent positive
10–14	91	91	6	6.6	85	7	8.2	14.2	77	7	9.1	22.0
15–19	480	480	66	13.7	345	39	11.3	23.4	378	54	11.7	36.1
20–24	95	95	18	19.0	66	9	15.8	31.7	54	6	11.1	39.2

T.P.T. (tablets). Age incidence. Same group as above

		0.0001 mgm./dose			0.001 mgm./dose				0.01 mgm./dose			
10–14	43	43	4	9.3	39	9	23.0	30.1	28	5	17.8	42.5
15–19	723	723	116	16.0	517	145	28.0	39.3	322	97	30.1	57.5
20–24	110	110	19	17.3	77	21	28.3	40.7	47	18	38.3	63.4

the 1/100,000 and 1/50,000 are combined we find that 25, or 8.4 per cent, reacted to O.T. of the 298 tested, while 67, or 22.4 per cent, of 298 reacted to the first test of T.P.T. (0.000,1 mgm.).

In lines C and D are the results of the 205 tested simultaneously with T.P.T. 0.001 mgm. and 1/10,000 O.T. Five times as many reacted to the T.P.T. as to the O.T., but again the T.P.T. dosage of total protein was 15 times as great, the almost identical ratio of both percentage reactors and protein per dose as was observed when O.T. 1/100,000 was compared with 0.000,1 mgm. T.P.T. These are the same individuals and the figures stand, but it must not be supposed that O.T. 1/10,000 will find only 5.4 per cent reactors. The figures in lines A and B are

unselected students in that this was their first test, and the percentage reactors is probably fair for such a sample of the population with the dilutions used. Those in lines C and D are a selected group, in that they were negative to both the O.T. and the T.P.T. given two days previously. Sixty-seven, or 22.4 per cent, of the series are eliminated from line C, and those below, by their reaction to the comparatively strong screening dose of T.P.T. 0.000,1 mgm., which in itself contained 1.5 times more protein than the second dilution of O.T. 1/10,000. Twenty-six more of the series

TABLE 3

First Group

Comparison of T.P.T. and O.T. tests done simultaneously on 298 students of group I

	MATERIAL	DILUTION	NUMBER IN SERIES	NUMBER TESTED	NEGATIVE	POSITIVE	PER CENT POSITIVE	ADJUSTED PER CENT POSITIVE	MATERIAL	DILUTION	NUMBER IN SERIES	NUMBER TESTED	NEGATIVE	POSITIVE	PER CENT POSITIVE	ADJUSTED PER CENT POSITIVE	
A.	T.P.T.	0.0001 mgm.	298	211	162	49	23.2	23.2	T.P.T.	0.0001 mgm.	298	87	69	18	20.7	20.7	Right arm
B.	O.T.	1–100,000	298	211	201	10	4.7	4.7	O.T.	1–50,000	298	87	72	15	17.2	17.2	Left arm

(Previously negative to both the T.P.T. and the O.T. above)

	MATERIAL	DILUTION	NUMBER IN SERIES	NUMBER TESTED	NEGATIVE	POSITIVE	PER CENT POSITIVE	ADJUSTED PER CENT POSITIVE OF SERIES	
C.	T.P.T.	0.001 mgm.	298	205	151	54	26.3	13.3	Right arm
D.	O.T.	1–10,000	298	205	194	11	5.4	4.26	Left arm

(Previously negative to all the T.P.T. and the O.T. above)

E.	T.P.T.	0.01 mgm.	298	127	86	41	32.3	61.1	Right arm
F.	O.T.	1–100	298	127	109	18	14.2	25.6	Left arm

are eliminated from lines C to F because they did not return for completion of the series of tests or because their subsequent tests with either the T.P.T. or the O.T. (to whichever they had failed to react) were not simultaneous with the next dilution of the other tuberculin. To include those subjects that in the second and third tests were being tested with only one of the tuberculins would introduce the possibility of previous tests heightening the level of sensitiveness, and so producing reactions that would not have developed in the absence of previous tests. While this possibility is still present in these tables marked "simultaneous tests."

still the two tuberculins have an equal chance to share in this phenomenon as they are treated exactly alike.

The final tests on 127 which had been negative to the first dilutions given on the first day, and the second dilutions given on the third day, and tested with the third dilution on the fifth day are presented in lines

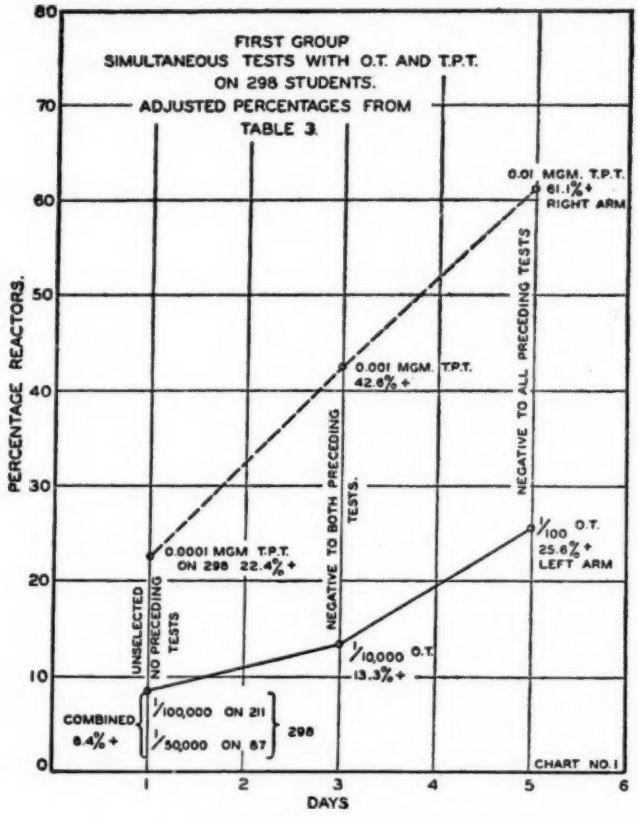

CHART 1

E and F. T.P.T. found 2.3 times more reactors, though it contained only 1.5 times more total protein per dose.

In order to determine how many of the series would have been positive to each tuberculin had all the negatives been tested with each of the stronger doses, we have had recourse to an assumption employed by Hart (6). In the column marked "Adjusted Percentage of Series" are the calculated percentages of the series that would have been found positive

had those not tested reacted in the same proportion as those that were tested with each dilution. The result is brought out better by chart 1 where the O.T.s, 1/100,000 and 1/50,000, are combined for the result of the first dilution of O.T. It will be noted that for the O.T. the percentage reactors start at 8.4 per cent for the first dilution, rise gradually through 13.3 per cent for the second dilution to 25.6 per cent for the total of the series for O.T. The behavior of the T.P.T. is in marked contrast, starting at 22.4 per cent and rising in an almost straight line through 42.6 per cent for the second dilution to 61.1 per cent for the series. It was thought that the rather unusual series of dilutions of O.T. might be the

TABLE 4

Second Group

O.T. and T.P.T. reactions obtained simultaneously in ascending doses from above downward, in 183 students of group 2

MATERIAL	DILUTION	NUMBER IN SERIES	NUMBER TESTED	NEGATIVE	POSITIVE	PER CENT POSITIVE	ADJUSTED PER CENT POSITIVE OF SERIES
T.P.T.	0.0001 mgm.	183	183	137	46	25.1	25.1
O.T.	1–10,000	183	183	144	39	21.3	21.3
	(*Previously negative to both of the above*)						
T.P.T.	0.001 mgm.	183	106	76	30	28.3	46.3
O.T.	1–1,000	183	106	93	13	12.2	30.9
	(*Previously negative to all of the above*)						
T.P.T.	0.01 mgm.	183	64	47	17	26.6	60.6
O.T.	1–100	183	64	61	3	4.7	34.1

explanation of this great discrepancy, so a new series was started on a second group of subjects.

This second group (183 high-school and nursing students) are shown in table 4, which is constructed like table 3 and with the same criteria for simultaneous tests. In table 4 each pair of lines represents simultaneous tests with the dilutions or dosages noted. In this table the ratio of protein content in the test-doses in the two tuberculins is maintained at a constant throughout the three dilutions. There is 1.5 times more total protein in the T.P.T. than in the O.T., each stronger dose of each tuberculin being just ten times the previous dose. The O.T. here and in group 3 is P.D. Rx 06559.

With this constant protein ratio, the T.P.T. found 1.2 times more reactors in the first dilution, 2.3 times more in the second and 5.7 times more in the third dilution. There is a growing disparity between the two tuberculins as the concentration of each is increased on the same scale. When the adjusted percentage for the series is calculated again on the assumption that those who were not tested would have reacted as those

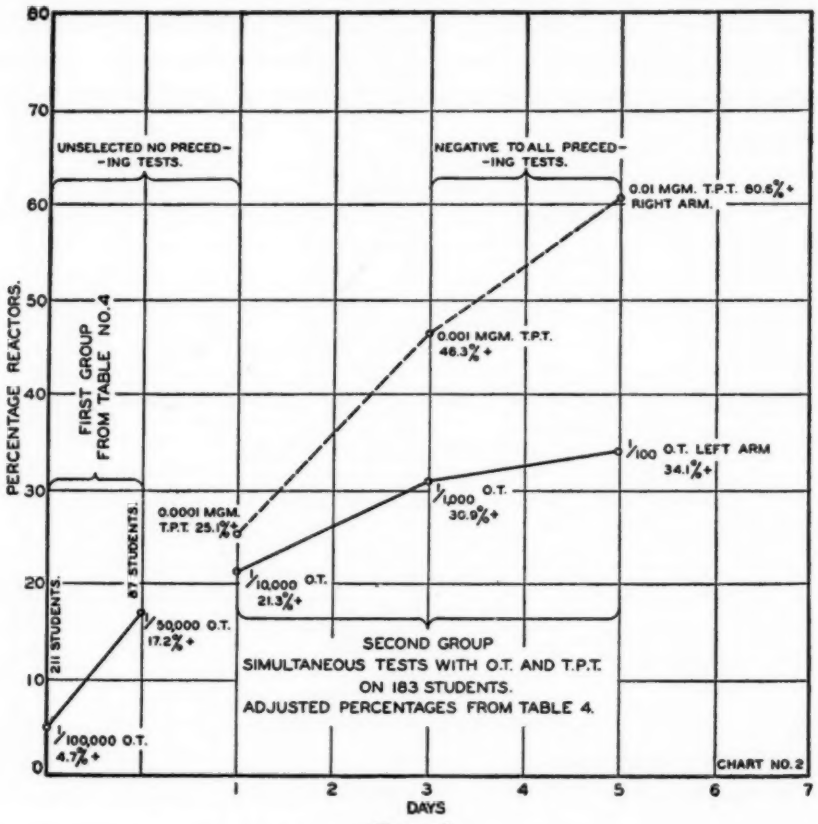

CHART 2

who were so tested, we find 60.6 per cent reacted to the T.P.T. while only 34.1 per cent reacted to O.T.

This fact is again represented in chart 2 where the curve for T.P.T. is seen to rise rapidly from 25.1 to 46.3 per cent for the second dilution, and then not quite so steeply to 60.6 per cent for the series. O.T. behaves very differently, showing a marked flattening of the curve as we go from

1/1,000 to 1/100. There has been imposed upon this graph the figures taken from the other group of students to obtain an idea of the lower end of the O.T. curve.

With such a curve for O.T. one can readily understand how it is safe to adopt Aronson's method of omitting the middle dilution of O.T. 1/1,000 in routine testing. We would not recommend dropping the middle dilution of T.P.T. for the difference between the weakest and strongest is too great.

Table 5 represents simultaneous tests done on 534 first-year college women (group 3) in September, 1933. The object in keeping this table

TABLE 5

Third Group

O.T. and T.P.T. reactions obtained simultaneously on ascending doses from above downward in 534 students of group 3

MATERIAL	DILUTION	NUMBER IN SERIES	NUMBER TESTED	NUMBER POSITIVE	PER CENT POSITIVE OF THOSE TESTED	ADJUSTED PER CENT POSITIVE OF SERIES
T.P.T.	0.0001 mgm.	534	534	87	16.2	16.2
O.T.	1–10,000	534	534	94	17.6	17.6
		(*Previously negative to both of the above*)				
T.P.T.	0.001 mgm.	534	363	101	27.9	39.6
O.T.	1–1000	534	363	45	14.4	29.5
		(*Previously negative to all of the above*)				
T.P.T.	0.01 mgm.	534	222	71	32.0	58.9
O.T.	1–100	534	222	18	8.1	35.2

separate, as well as the corresponding chart 3, is to show the striking constancy of the behavior of two different lots of T.P.T. tablets tested in two different years on similar groups and controlled by the same lot of O.T. Again about 60 per cent react to the three dilutions of T.P.T. as compared to about 35 per cent to O.T. The T.P.T. curves represented in chart 3 are almost identical to the other two groups. The age incidence in this case is of course almost identical to that in group 1, done one year earlier. The difference between the two tuberculins is slight in the weaker doses, but in the stronger doses the difference is marked and constant.

ANALYSIS

The great difference in percentage reaction between small doses and large doses reported here is not confirmed in surveys in districts highly tuberculized. The difference we are reporting will appear only in groups of subjects less sensitive to such weak doses as 1/10,000 O.T. Obviously if 30–80 per cent react to O.T. 1/10,000 there is less room for added reaction to stronger doses, so that the percentage increment is less impressive.

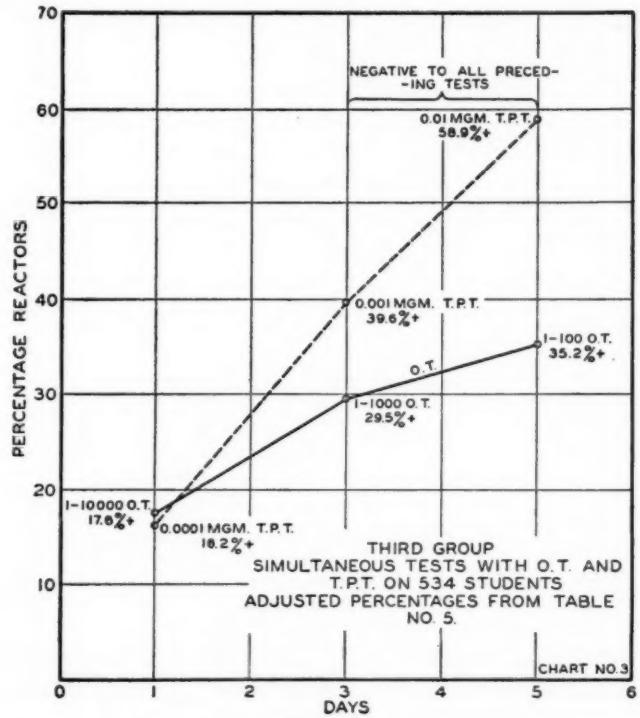

CHART 3

Through three approaches we attempted to learn why T.P.T. found more reactors than O.T. The first was to test 50 tuberculous patients with blank milk-sugar tablets made exactly as the T.P.T. tablets but without the protein. No patient reacted.

The second approach was an attempt by several methods to learn whether the preliminary tests might sensitize the subject and so give false positives in the second and third tests. The third approach was

through the hope that X-rays of the chest in individuals negative to one tuberculin but positive to the other might show one of the tuberculins to be in error.

SENSITIZATION

The sensitization question is a serious one. Seibert (11) (12) has been able to sensitize guinea pigs with as few as three intracutaneous injections of T.P.T. at weekly intervals, given 10 mgm. at each injection. In an effort to arrive at some conclusion as to this possibility on humans we carried out a suggestion made by Max Pinner, of testing new-born infants. Here the question of possible infection could not enter. Table 6 shows the results of these tests. Thirty-nine infants were tested with

TABLE 6

39 newborn babies remaining negative (no sensitization) to repeated tuberculin tests

NUMBER OF BABIES	TOTAL TESTS	NUMBER OF TESTS WITH T.P.T. IN MGM.			NUMBER OF TESTS WITH O. T. DILUTIONS			DAYS ELAPSED BETWEEN FIRST AND LAST INJECTION	AGE IN DAYS AT FIRST TEST
		0.0001	0.001	0.01	1/10,000	1/1,000	1/100		
1	18	3	3	3	3	3	3	42	2
2	12	2	2	2	2	2	2	19 and 23	21 and 18
2	10	2	2	1	2	2	1	10	1 and 4
2	8	1	1	2	1	1	2	10 and 23	22 and 1
2	8	2	1	1	2	1	1	8	4
1	6	2	0	1	2	0	1	10	
20	6	1	1	1	1	1	1	4, 6, 7 and 8	2 to 50
4	4	0	1	1	0	1	1	3	2 to 36
5	4	1	1	0	1	1	0	2	1 to 5

the same series of three tests of each tuberculin that we used on the students, not one showing a reaction. One infant had as many as 18 tests within 42 days, and two had 12 tests each during a shorter period. It may be of course that infants are more difficult to sensitize than adults, but we have had a similar experience with students and nurses.

In a group of 73 students and nurses who received 7 or more tests over a period of one to twenty months there were 46 who remained negative. One nurse received 24 tests, 12 O.T. and 12 T.P.T. or 4 complete series within 5 months and remained negative. Twenty-seven of the 73 became positive. Eleven of these were college women but 16 were nurses in contact with tuberculosis patients. Ten of the 27 became positive to T.P.T. alone but 16 became positive to both O.T. and T.P.T.

Also, it seems that if these individuals were being sensitized by repeated injections, the curve representing the percentage reactors would be flat or nearly so for the first two injections, suddenly rising on the third injection as suggested by Seibert's findings (11) (12) in guinea pigs. There are only five days between the first and last injection in one complete series of tests, and it must be admitted that this is a brief period in which to expect sensitization to develop.

TABLE 7

Twenty-one subjects tested to show the effect of the omission of preliminary T.P.T. tests, hypersensitive subjects eliminated by use of usual O.T. dilutions

DAY OF TEST	RIGHT ARM		LEFT ARM	
	T.P.T. (P.D. & Co. Tablets)		O.T. (P.D. & Co. Stock)	
			1–10,000	
			Positive	Negative
1st	No test given		2	19
	(*Previously negative to above*)			
			1–1000	
3rd	No test given		3	16
	(*Previously negative to above*)			
	0.001 mgm.		1–100	
	Positive	Negative		
5th	4	11*	3	13
	(*Previously negative to all above*) (*one exception*)*			
	0.01 mgm.			
7th or 8th	5*	7	No test given	

* One negative to O.T. 1–100 reacted to T.P.T. 0.01 mgm. but was not tested with 0.001 mgm. T.P.T.

The following critical experiment was suggested by Seibert to determine the rôle of sensitization in producing the discrepancy between T.P.T. and O.T. found in our tables. It was noted that the greatest difference in the two tuberculins occurred in the final tests. Those reacting to the final T.P.T. and not to the final O.T. might then be explained as having been sensitized by the two previous T.P.T. tests. It was therefore suggested that if the preliminary T.P.T. injections be omitted then the reac-

tion produced by the final T.P.T. could not be due to sensitization. Twenty-one students who had never received T.P.T. were selected for the experiment. In the left arm they received the usual three dilutions of O.T., 1–10,000 on the first day, 1–1000 on the third day and 1–100 on the fifth day, as in our previous O.T. testing. Nothing was injected in the right arm on the first or third day. On the fifth day those negative

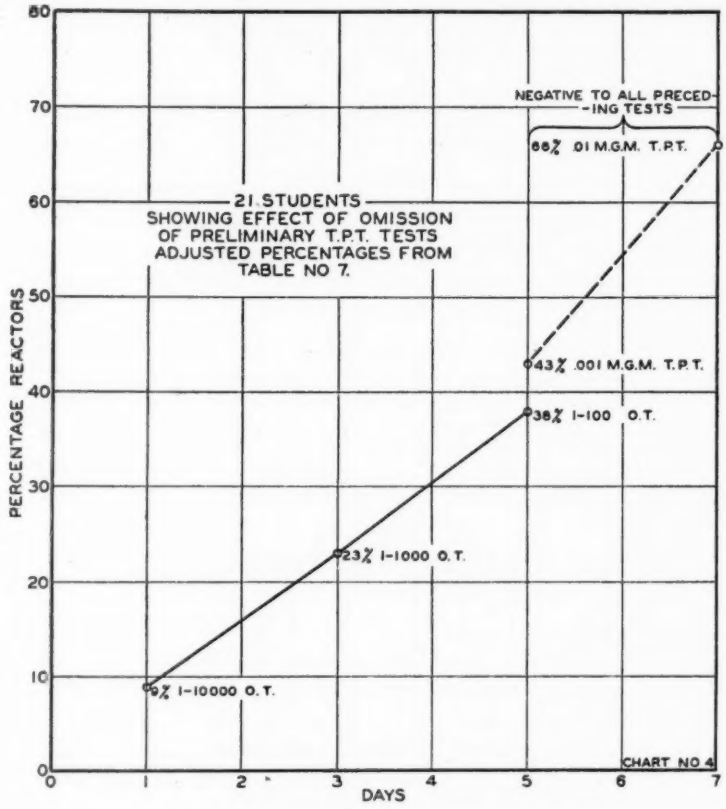

CHART 4

to O.T. 1–1000 received in the right arm 0.001 mgm. T.P.T., simultaneously with the O.T. 1–100 in the left arm. No further O.T. was given, but on the seventh or eighth day 0.01 mgm. T.P.T. was given in the right arm of those negative to the 0.001 mgm. T.P.T. The figures for this are shown on table 7. Of twelve negative to O.T. 1–100, six became positive to T.P.T. Four of the six had had one test with T.P.T. 0.001 mgm., 2 to 3 days before the final T.P.T. Two of the six had had no

previous T.P.T. whatever. These two assume an additional importance in that the T.P.T. to which they reacted contained only 0.15 of the total protein in the O.T. 1–100 to which they failed to react. These results are better shown graphically on chart 4.

To test this question still another way, we tested 37 students, using O.T. in the left arm in the usual three dilutions. In the right arm instead of omitting injections on the first and third days we used a tuberculin recently available (SOTT or Purified Protein Derivative) which

TABLE 8

Thirty-seven subjects tested to show the relation between O.T., Purified Protein Derivative, and T.P.T.

DAY OF TEST	RIGHT ARM				LEFT ARM	
	T.P.T. (P.D. & Co. Tablets)		(P.D. & Co. Tablets) Purified Protein Derivative		O.T. (P.D. & Co. Stock)	
			0.000,02 mgm.		1–10,000	
			Positive	Negative	Positive	Negative
1st			6	31	6	31
(Previously negative to both above)						
			0.005 mgm.		1–1000	
3rd			1	28	1	28
(Previously negative to all of the above) (except one which did not get test on the 3rd day)						
	0.01 mgm.				1–100	
	Positive	Negative				
5th	14	14			2	26
Total.....	14	14	7	28	9	26

Seibert (12) (13) has shown to be practically free of sensitizing ability either to itself or to T.P.T. This freedom from sensitizing power she has correlated with its molecular weight which is considerably lower than that of T.P.T. The Purified Protein Derivative is the tuberculin recently recommended for general use by the Research Committee of the National Tuberculosis Association (15). The doses were 0.000,02 mgm. on the first day and 0.005 mgm. on the third day. For the final test on the right arm 0.01 mgm., T.P.T. was used at the same time as the O.T. 1–100 in the left arm. Twenty-

eight subjects failed to react to either the 0.005 mgm. Purified Protein Derivative or to O.T. 1–1000, but fourteen of this twenty-eight did react to 0.01 mgm. T.P.T. two days later. Of the 14, only 4 had had T.P.T. previously, and that one year earlier, three of these having been positive at that time. Of the 26 negative to O.T. 1–100, twelve became positive to T.P.T. 0.01 mgm. The results of this are shown in table 8, and graphically on chart 5.

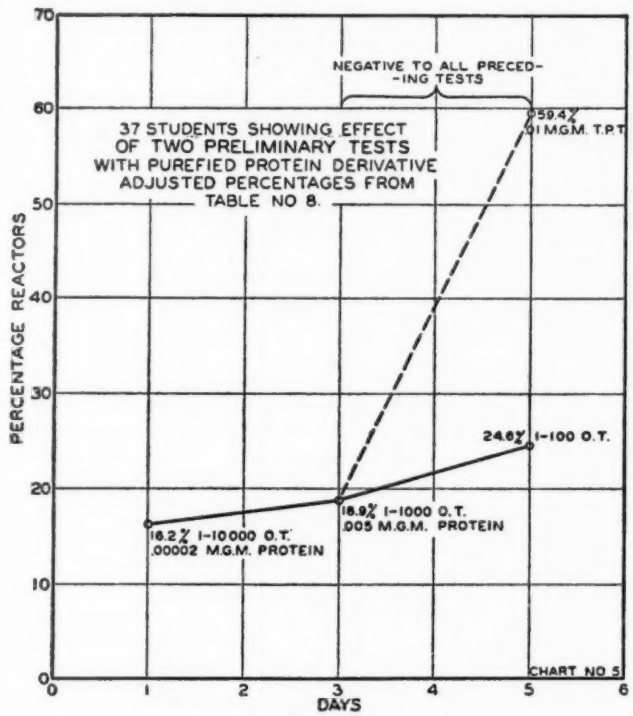

CHART 5

While sensitization with T.P.T. is a proved fact in animals with larger doses and the possibility in human beings is suggested by our figures, we fail to find it under controlled conditions in the newborn, and, when the possibility is removed by omitting sensitizing doses, we still find the almost identical discrepancy between T.P.T. and O.T. Sensitization, then, while still not disproved as a possibility in the human being, cannot be the explanation of the fact that many more react to T.P.T. than to O.T. in the doses we used.

SPECIFICITY

The attempt to explain the discrepancies by the X-rays of the chest presents many difficulties. If the tuberculous infection has left undoubted calcified scars in visible portions of the X-ray film then that evidence can be used to confirm a positive tuberculin reaction, if either tuberculin reaction is positive. If neither tuberculin is positive the X-ray evidence must mean that the doses used were insufficient to detect the dormant sensitiveness of that subject, that both tuberculins lack potency, or that sensitiveness has completely disappeared. On the other

TABLE 9

27 student nurses remaining negative (no sensitization) to repeated tuberculin

NUMBER OF NURSES	TOTAL TESTS	NUMBER OF TESTS WITH T.P.T. MGM.			NUMBER OF TESTS WITH O.T. DILUTION			NUMBER OF TESTS WITH T.P.U. MGM.			MONTHS ELAPSED BETWEEN FIRST AND LAST TESTS
		.0001	.001	.01	1/10,000	1/1,000	1/100	0.00001	0.0001	0.001	
1	24	4	4	4	4	4	4	0	0	0	5
1	17	3	3	2	2	2	2	1	1	1	13
2	15	2	2	2	2	2	2	1	1	1	20
1	14	3	2	2	3	2	2	0	0	0	1
2	13	2	2	1	2	2	1	1	1	1	20
1	12	2	2	2	2	2	2	0	0	0	1
1	11	2	1	1	2	1	1	1	1	1	
1	10	2	2	1	2	2	1	0	0	0	2
1	9	1	1	0	1	1	0	2	2	1	
1	8	2	2	1	1	1	1	0	0	0	
5	7	1	1	0	1	1	0	1	1	1	
4	7	2	2	1	1	1	0	0	0	0	
2	6	1	1	0	1	1	0	1	1	0	
4	5	2	1	1	1	0	0	0	0	0	
2	5	1	0	0	1	0	0	1	1	1	
2	5	1	0	0	1	0	0	1	1	1	

hand the most frequent result is that the X-ray film shows no evidence whatever of tuberculous infection, past or present. This is negative evidence and is useless as a control, for the remnant of the infection may be invisible in the X-ray or may be in any other part of the body. Only "positive X-rays," as defined above, can be considered as a control in any sense. Furthermore "positive X-rays" in subjects reacting to both tuberculins do not serve to elucidate the difference in the tuberculins. We have eliminated then all but the "positive X-rays" on those subjects in whom the strongest doses of either tuberculin failed to produce a

reaction. Out of the 501 subjects X-rayed, 95 showing positive evidence of tuberculous infection, all are eliminated on the above grounds save the following 20 discrepancies:

Seven with "positive X-rays" were negative to T.P.T. 0.01 mgm. and O.T. 1–100 (5 P.D. and 2 Aronson).

Twelve with "positive X-rays" reacted to T.P.T. (5 to 0.001 mgm. and 7 to 0.01 mgm.) but not to O.T. 1–100 (9 P.D. and 3 Aronson).

One with a "positive X-ray" reacted to O.T. 1–1000 (P.D.) but not to T.P.T. 0.01 mgm.

These results mean that T.P.T. finds more subjects with X-ray evidence of tuberculous infection. The objection is made that any substance to which more people will react will find more positive X-rays on the basis of probability. As sensitization seems an inadequate explanation the question is raised as to the specificity of T.P.T.

The specificity of O.T. is accepted now on evidence accumulated over nearly half a century. Even this evidence is not absolutely conclusive, as there are no Koch's postulates formulated for the establishment of specificity in skin sensitiveness. The evidence for O.T. is summarized by Hart (6):

1. Correlation between necropsy evidence and tuberculin reaction during life.
2. Correlation between autopsy statistics and incidence of positive tuberculins in the same periods and in the same samples of population.
3. Evidence that both the incidence of positive tuberculins and latent pulmonary foci increase with age, and that the frequency of both is greater among contacts than noncontacts.
4. Animal experimentation demonstrating that infection induces skin sensitiveness to O. T.

The first two above, using autopsy evidence, will require years for any new tuberculin such as T.P.T. to be established on the same grounds as has O.T. The third requires the elaborate use of X-rays on many thousands and can be accumulated only with more years. The animal demonstration for the specificity of tuberculin protein has been done by Seibert (14) and others. For the immediate proof of specificity of T.P.T. in human material one is forced to accept only evidence of its correlation with O.T. The correlation is adequately established in the weaker doses of each. In our own figures every subject reacting to T.P.T. 0.000,1 mgm. reacted also to some dilution of O.T. if tested up to 1–100. This appears to establish the specificity of the substance as identical with

O.T. If multiplication of the concentration of T.P.T. in the test dose provokes reactions that do not appear with the same multiplication of O.T. it does not necessarily mean that concentration destroys specificity or provokes nonspecific reactions. It may as readily mean that as T.P.T. is a pure protein it is susceptible of a concentration of specific substance which is impossible in O.T. In one case of tuberculosis of the skin, proved by biopsy, 1 mgm. of T.P.T. gave a typical reaction while 1/10 cc. of undiluted O.T. failed to do so. Thus it has been easily and adequately demonstrated that every proved case of clinical tuberculosis reacts to some dose of T.P.T., but the reverse, that every person so reacting has been infected, is almost impossible of unequivocal proof.

There is no reason to believe that skin sensitiveness does not fluctuate through the stronger concentrations as it is known to do through the weaker concentrations. It surprises no one that a person reacting to 1–10,000 O.T. may require 1–100 O.T. for a reaction at some later date. We have had two students to react to 0.01 mgm. T.P.T. one year who failed to react to the same dose one year later, and failed on both occasions to react to O.T. 1–100. It may be that by further increasing the doses of T.P.T., as Hart did with O.T., we will find the curve flattening out at some point under 100 per cent, and that percentage will be our true incidence of tuberculinization instead of that now assumed on the basis of O.T. Obviously, if the curve does not flatten the uselessness of T.P.T. as an indicator will be demonstrated. Until such an opportunity is taken advantage of, the specificity of T.P.T. can be accepted as equal to O.T.

As we found no instance of a student with active disease which did not react to a weak dose, it may be asked what advantage is gained by a tuberculin more potent than O.T. It seems to us to depend upon the use to which the tuberculin is to be put. Surveys to find those students in need of treatment have been well served by O.T. A stronger tuberculin is not needed for such a purpose. But when we are in danger of having different schools of therapy built upon the sole distinction of first infection and second infection, then we need a tuberculin that will enable us to segregate with accuracy the infected from the noninfected. As stated in the opening paragraph of this paper, we undertook this study to select a tuberculin that would enable us to make such a distinction. Therefore we regard T.P.T. as most nearly meeting the requirements for the study of this problem.

CONCLUSIONS

1. T.P.T., a tuberculin protein of medium molecular weight, in dry powder can be incorporated in minute amounts (0.001 mgm.) in tablets of dry milk sugar, with an accuracy comparable to that obtained by the dilution of O.T. by quantitative chemical methods.

2. The milk sugar alone produces no reaction in tuberculosis patients.

3. Among those reacting to either T.P.T. or O.T., the percentage of severe and mild reactions is about the same when roughly comparable protein doses are used.

4. T.P.T. 0.000,1 mgm. is equivalent in potency to 0.1 cc. of 1/10,000 O.T. in terms of percentage reactions among students.

5. Every student reacting to T.P.T. 0.000,1 mgm. reacted to O.T. in some dilution up to 1/100.

6. Every patient with proved tuberculosis (about 100) including skin tuberculosis, reacted to some dose of T.P.T. up to 1.0 mgm.

7. As the dose of O.T. and T.P.T. are increased in multiples of 10, many more students react to T.P.T. than to O.T.

8. Twelve reacting to T.P.T. and not O.T. had evidence of previous tuberculous infection in the X-rays. One with such evidence reacted to O.T. but not to T.P.T. and seven were negative to both tuberculins (T.P.T. 0.01 mgm. and O.T. 1/100).

9. We have presented evidence to show that sensitization does not account for the differences in number of reactions between O.T. and T.P.T.

10. It is suggested that comparison of percentage reactors in simultaneous tests on apparently healthy individuals is a delicate method of standardization of an unknown against a known tuberculin.

11. T.P.T. in doses used suggests that tuberculization in this community is at a higher level than indicated by O.T. 1/100.

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BLOOD GLUTATHIONE IN TUBERCULOSIS

RUSSELL N. LOOMIS[1] AND EMIL BOGEN[1]

The active sulphydryl compound, *glutathione*, was discovered in yeast cells and animal tissues more than a decade ago (1), but only recently has its chemical composition been established (2) (3) (4). The readiness with which this substance participates as an intermediary in tissue oxidations (5) (6), and its widespread distribution throughout the body (7) justify the emphasis that has been placed upon its biological importance. Variations in the glutathione content of various tissues have been found to be related to their metabolic activity (8) as well as to their rate of growth (9). Earlier studies failed to show the presence of glutathione in the blood (7), but it is now known to be present (10), particularly in the red corpuscles (11), where it forms a considerable part of the nonfermentable reducing substance of the blood (12).

Most of the glutathione in the blood is found to be in the reduced state, but treatment of blood filtrates with zinc-dust or other reducing agents will increase the apparent amount present by about five mgm. per 100 cc. (13). Since in arterial blood (14) or after aeration (15) the amount of reduced glutathione obtained by titration is lessened, this difference has been attributed to the presence of a small amount of oxidized glutathione. Although this conclusion has been challenged (16) and the identification of the substance responsible for the increased titration figure after zinc treatment requires further investigation, its actual occurrence is established.

There is a widespread clinical impression that tuberculosis is accompanied by interference with the metabolic processes, resulting in the accumulation of incompletely oxidized materials in the blood-stream. The slightly lowered carbon-dioxide-combining power in the blood in pulmonary tuberculosis (17), the lowered vital capacity of the lungs (18), and the increased lactic acid content of the blood (19) are consistent with the idea of suboxidation in tuberculosis, but there has been, as yet, no direct evidence of its existence. Tuberculous tissues have been reported to be deficient in reduced glutathione (20) (21), but the few analyses

[1] Olive View, California.

available fail to show any consistent change in the glutathione content of the blood (22) (23). Deficient aeration, or toxic interference with oxidations in the body, might be expected to increase the proportion of the glutathione of the blood that is present in the reduced state and diminish the fraction remaining oxidized. As no data could be discovered in the literature upon this point, an experimental investigation was initiated.

Both reduced and total glutathione were determined according to the method of Woodward and Fry (24), the only modification being that the

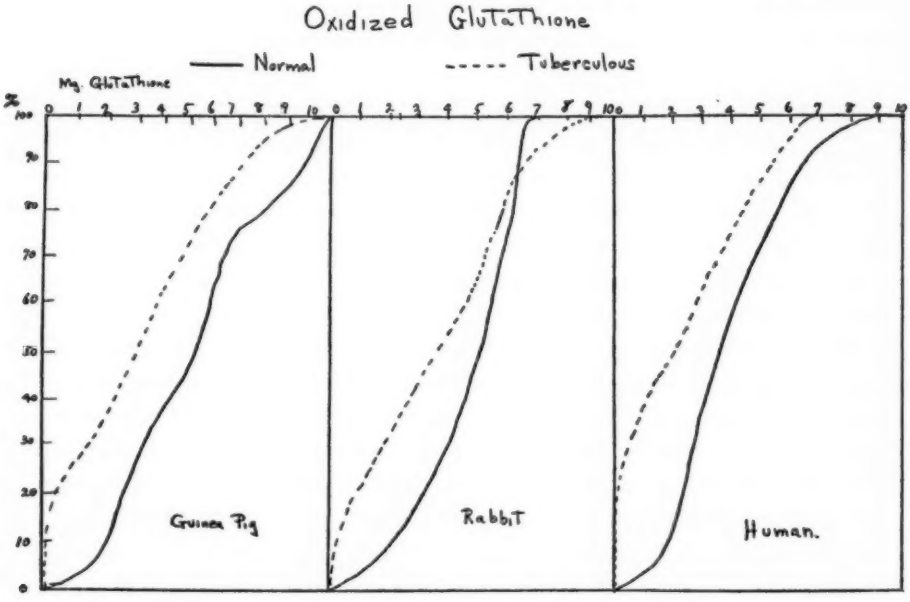

CHART 1
For description see text

blood was centrifugated instead of filtered, as suggested by Benedict (25), in order to lessen the time required for the obtaining of a clear filtrate. Ten-cc. portions of the sulphosalicylic-acid filtrate of oxalated venous blood were titrated with potassium iodate before and after treatment with zinc-dust, the reduced and total glutathione content of the blood calculated accordingly, and the difference expressed as "oxidized glutathione." The animals were bled from the right side of the heart under ether anaesthesia, the human beings from the cubital vein, and the filtrates made without delay.

Fifty normal guinea pigs, taken for controls, gave an average of 62 mgm. reduced glutathione per 100 cc. of blood, which was increased to an average of 68 mgm. after treatment with zinc-dust. The difference, which may be regarded as oxidized glutathione, averaged 6 mgm. and in no instance was it entirely absent. More than 120 guinea pigs were then studied which had been infected with virulent human tubercle bacilli subcutaneously from six to fourteen weeks previously. Both the reduced and the total glutathione were higher in this group than the corresponding figures for the normal guinea pigs, but especially striking was the diminution in the difference in the titration caused by treatment with zinc. More than a sixth of them showed no such difference at all, and the aver-

TABLE 1

Blood glutathione in tuberculosis

	REDUCED GLUTATHIONE		TOTAL GLUTATHIONE		DIFFERENCE	
	Mean	± Standard deviation	Mean	± Standard deviation	Mean	± Standard deviation
Guinea-pigs						
Normal	62	6	68	6	6.5	5.0
Tuberculous	69	7	72	7	3.5	3.0
Rabbits						
Normal	38	4	44	4	6.0	2.0
Tuberculous	43	6	48	7	4.0	3.0
Human						
Normal	34	7	38	7	4.5	2.0
Tuberculous	41	5	43	5	3.0	2.0

age of the entire group was nearly half that of the normals. Although there is much overlapping between the two series, the increase in the total and reduced glutathione and particularly the lessening in the difference between them appears quite definite and suggests an actual condition of suboxidation in this disease. The differences appear somewhat more marked among the guinea pigs in whom the disease had progressed for a longer time.

Similar analyses made upon 16 normal rabbits, and then again on the same animals one month and two months after they had been infected with human tubercle bacilli, showed similar differences. As rabbits tend to recover from this infection, it was noted that the figures for the

second month returned nearer to the initial values. The absolute figures for reduced glutathione in the rabbits was considerable less than that found in the guinea pigs, but the oxidized glutathione lay in the same range.

Similar determinations performed on the venous blood of 24 apparently healthy laborers and of 16 school children gave figures corresponding with those reported by other workers with this method (24), averaging 34 mgm. of reduced glutathione and about 4.5 mgm. of oxidized glutathione. The children showed somewhat lower reduced glutathione values than did the adults, which can be partially attributed to their lower haemoglobin content, and lower red blood cell counts.

Forty-eight patients suffering with advanced pulmonary tuberculosis showed the same differences as had been observed among the animals,—an increase in the reduced glutathione and a lessening in the difference caused by zinc treatment of the filtrate. Without committing ourselves at this time as to the exact nature of the material causing this difference, it may be urged that its diminution or disappearance indicates a lowering of the oxygen tension of the blood or tissues, and may be taken as an index of suboxidation in the body. With this in mind, it is interesting to note that there appears to be a consistent diminution in its appearance in the presence of tuberculosis in guinea pigs, rabbits and man. It is particularly notable that in a considerable proportion of the tuberculous bloods in all three species, about one-fifth of them in fact, no such substance appeared to be present at all, while in the normal bloods this was practically never encountered. The apparent increase in the amount of reduced glutathione in these tuberculous bloods is consistent with the idea that there is here a reduction of part of the glutathione normally remaining in the oxidized form, while the slight increase in the total glutathione may represent a defense reaction attempting to compensate for it, or perhaps merely an effect of the loss of this substance from the tuberculous tissues.

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A NEW MEDIUM FOR THE RAPID CULTIVATION OF TUBERCLE BACILLI[1]

ALFRED GUERNON

The characteristic slowness of growth of tubercle bacilli has been a handicap to both the bacteriologist and the physician. Little progress has been made in accelerating the speed of growth of the bacillus directly from infected material.

Corper (1928), describing his own medium, says that incubation of 2–6 weeks is necessary for obtaining a luxuriant elevated growth of tubercle bacilli. Sweany and Evanoff (1928) reported on a medium of their own composition that growth is visible at the earliest on the 13th day, the mean period being 28 days and the longest 36 days. Malkani (1929) gives superiority to the medium of Corper-Uyei's medium over that of Petroff in regard to rapidity of growth. He states that approximately 4–6 weeks are required to develop cultures made from infected tissues. Woolley and Petrik (1931) were able, on a medium devised by them, to obtain a growth from sputum on an average of 21 days. Finally Shaffer, making a comparative study of various media, concluded that the media of Corper, Uyei and Petragnani were far superior to the other media used. He noted that colonies were frequently visible in 2–3 weeks and almost always by the end of the 4th week.

With a view to improving the rapidity of growth, experiments were conducted in the present study for the purpose of devising a medium that would give a growth in a shorter time, if possible. After some initial experiments the medium finally adopted is as follows:

Agar 0.86 per cent; same amount of peptone; 1.73 per cent potato meal; 3.48 per cent glycerine and 26.09 egg, with the addition of gentian-violet 1-30,000, —put up in tubes, as a more convenient method.

[1] From the P. E. Lichtenhein Memorial Laboratory, Mt. Sinai Sanatorium, Ste Agathe, Quebec, Canada.

Preparation of the Medium

(1) Dissolve, as completely as possible, by stirring with a glass rod, 10 gm. of potato meal and 5 gm. of peptone in a beaker containing 385 cc. of distilled water.

(2) Add 5 gm. of agar, and heat mixture to boiling point, till agar is completely dissolved.

(3) Cool to 65°C., and then add a mixture containing 20 cc. of glycerine, 150 cc. egg and 1.8 cc. of a 1 per cent alcoholic solution of gentian-violet (previously filtered).

(4) Filter mixture.

(5) Tube in quantities of 7–8 cc. and slant.

(6) Inspissate for two hours at 70°C. on the first day and one hour on second day.

As, in our experience contamination occurred only during the inoculation of the tubes, we did not test our medium for sterility.

Technique

Fresh sputum, containing varying numbers of bacilli was treated according to Petroff's (1915) method: 4 per cent sodium hydroxide incubated, centrifugated and an addition of 7 drops of normal hydrochloric acid to every cubic centimetre of the mixture, again centrifugated for 15 minutes and the sediment planted, a single loop on the surface of the medium. Ordinary corks were used, sealed with paraffin and incubated, sloping surface down. The last step being important in order to prevent excessive moisture.

Experiments

Three final experiments were conducted and the results were recorded as in the accompanying tables.

Forty-two specimens were prepared and inoculated according to the above-mentioned technique. They were examined daily from the fourth day, and, when evidence of growth was noticeable, smears were made and examined in the usual way. Washing the surface of the growth with saline solution instead of scraping in order to obtain smears was occasionally done with success.

TABLE 1

SPUTUM NUMBER	APPARENT GROWTH: NUMBER OF DAYS	EASILY VISIBLE GROWTH: DAYS	CONTAMINATIONS
1	6	6	none
2	6	7	
3	6	7	
4	5	7	
5	6	9	
6	6	8	
7	7	9	
8	5	7	
9	6	6	
10	6	8	
11	6	9	
12	7	9	
13	6	8	
14	6	9	
15	6	7	

TABLE 2

SPUTUM NUMBER	APPARENT GROWTH	EASILY VISIBLE GROWTH	CONTAMINATIONS
	days	*days*	
1	4	5	
2	4	5	
3	5	7	
4			contaminated
5	5	5	

TABLE 3

SPUTUM NUMBER	APPARENT GROWTH	EASILY VISIBLE GROWTH	CONTAMINATIONS
	days	*days*	
1	4	5	none
2	6	7	
3	5	7	
4	6	7	
5	6	7	
6	4	5	
7	4	5	
8	6	7	
9	4	5	
10	4	5	
11	4	4	
12	7	9	
13	4	6	
14	4	6	
15	5	7	
16	5	5	
17	5	5	
18	7	9	
19			contaminated
20	5	5	
21	4	5	
22	6	6	

Growth in all but two tubes by the 14th day was in the form of numerous colonies, and luxuriant on the 21st day.

SUMMARY AND CONCLUSIONS

The object of these experiments was to find a medium that would produce a growth of tubercle bacilli more quickly than the widely used media. Of 42 specimens containing few or many bacilli all except two which were contaminated gave visible evidence of growth before the 7th day and in many instances as early as the 4th day, the average being six days.

From these results it is evident that this medium has a distinct value because of its certainty and consistency in producing positive findings, but, most of all, because it produces a rapid growth; it is easily prepared; it is inexpensive; and attempts to grow tubercle bacilli from ordinarily negative sputum have been very encouraging.

The author wishes to thank Dr. D. L. Mendel, Dr. N. Lewin and Mr. Hyman Spier for their valuable assistance and advice.

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THE IMPORTANCE OF SOCIAL DIAGNOSIS IN THE TREATMENT OF THE TUBERCULOUS

BEULAH BURHOE

The good physician has always treated the man, not his disease. He has known that hopes, fears, sorrows and joys are more potent forces than powders and pills, and that even the most meticulous medical attention will not save the man who does not want to live. The old family doctor tying his buggy at the front gate came as a family counselor. He knew that the cupboard would be empty if the farmer couldn't plow his fields. He understood all the domestic hurdles that must be conquered before the sick man could give himself up to treatment. The modern doctor knows all this as truly as his country predecessor did and in private practice he usually is still the wise family friend.

The situation is very different, however, in an institution. The physician in charge of a tuberculosis sanatorium, for example, knows well that the progress of many a patient is retarded by the state of his mind. He knows that worry about the rent, the grocery bill, the children's health, inoculates many a patient against successful medical care. But because he is only one human being with only twenty-four hours a day at his disposal, he cannot unaided act as personal counselor to his large sanatorium family. He must have help from the social agency, the educator, the vocational guide and the rehabilitation specialist in order to safeguard the expensive medical investment of sanatorium treatment.

That tuberculosis patients have social hazards is shown by the findings of some of the recent studies made by the Rehabilitation Department of the National Tuberculosis Association. Five thousand cases in 40 sanatoria were interviewed by trained workers to ascertain educational background, previous occupations, plans for future employment and desires for academic and vocational education. It was found that 60 per cent had gone no further than the eighth grade in school, many stopping years before that and a considerable number having had no schooling at all. Since ordinary day's labor is usually contraindicated for persons who have had tuberculosis, and since for the greater part of this large

group more suitable work from the physical standpoint is ruled out because of lack of training, these patients can be said to have two handicaps, the educational as well as the physical.

Sixty per cent of the group studied (all above 15 years of age) were between 16 and 35, and 80 per cent were under 45 years of age. They belong therefore to the young wage-earning and child-rearing group.

Before entering the sanatorium they had been engaged in more than 250 different kinds of work ranging from embalming to aviation but falling mostly into the unskilled groups. Only 38 per cent wished to return to their former occupations, while 48 per cent either hoped to change to an entirely different type of work or had no idea of what they would or could do. Many of the employment choices showed discouraging ignorance. A large number apparently still have faith in that old chimera, a "light out-door job." Others hoped to leave an occupation basically suitable, like stenography, for the gambles of poultry-raising and truck-farming. An alarmingly large number wished to be cooks, waiters, nursery governesses, and teachers of small children. It can be fairly said that the majority of these patients are in urgent need of sound vocational advice.

Fifty-six per cent of the group expressed a desire to study while in the sanatorium. They were keenly conscious of the fact that a limited educational background is a serious vocational handicap.

Thirty per cent of the requests for instruction were for commercial subjects, typing, shorthand, bookkeeping, accounting and office practice; 14 per cent for household arts, including cooking, sewing and child care; 12 per cent for vocational subjects such as draughting, mechanics, radio; 9 per cent for academic subjects of high-school grade; 8 per cent for English for the foreign-born. The remaining 27 per cent of requests were for miscellaneous kinds of training from barbering to the highest level of university work.

The 40 institutions studied, including state, county and municipal sanatoria, are located in 14 states representing all parts of the United States except the south, so that the data can be considered a true random sampling of the general sanatorium population of the country.

The basic conclusions of this study are therefore that the sanatorium population in the United States is made up principally of young people with very limited education, with inadequate vocational training and varied occupational experience, greatly in need of good vocational advice and eager to learn. The provision of vocational guidance and of suit-

able academic and vocational education for sanatorium patients are indicated as steps in the solution of some of the social problems of the tuberculous.

A survey of the field reveals the encouraging fact that in over 50 sanatoria in 17 states there is some provision for adult education. These educational departments vary from the teaching of a few subjects by patient volunteers to a well-organized school offering elementary- and secondary-school subjects, vocational training and work on the university level, and manned by trained teachers whose salaries are paid by the regular school authorities. In about a third of the group financial support comes from the city or county Board of Education. The others are maintained by the sanatorium, the local Rehabilitation Bureau, the tuberculosis association, or combinations of these.

The subjects while varied are predominantly of high-school grade, the commercial subjects being outstandingly popular. There is a comforting absence of those studies which hang on the fringes of education. Patients seem to be aware of the practical nature of their intellectual needs. This is indeed a contrast to the older type of teaching in the sanatoria where the main emphasis was placed upon the creation of baskets, leather key-holders, rugs and lampshades of doubtful usefulness and beauty and saleable only for "sweet charity's sake."

A survey of the present status of occupational therapy shows that approximately 90 sanatoria have occupational-therapy departments. The subjects taught are almost entirely the handicrafts with leather work and basketry far in the lead. It is interesting to note that 65 per cent of these departments have been in existence for more than five years and 41 per cent for more than ten years, while more than two-thirds of the departments of adult education previously discussed have been organized less than five years. There would seem therefore to be a general trend for handicraft occupational therapy to be supplanted by academic and vocational education.

Dr. Horace LoGrasso, of the J. N. Adam Memorial Hospital, says of study:

> It gives the patient hope and encouragement and thus tends to hasten his recovery, by the knowledge that his vocational training is fitting him for some future useful activities. The fact that he is learning something whereby he will be able to earn his living after he leaves the hospital helps him to sustain his morale and helps him to take an active interest in his work. We have actual proof that many of our ex-patients are now earning their living through

the vocational training they received at this hospital. Those patients whose high school work has been interrupted by illness can also complete their counts at this hospital. While craft and handiwork are interesting and useful to a certain extent, this training means practically nothing to a patient after he leaves the hospital—as far as earning his living is concerned.

While the providing of opportunities for formal education is a new movement, individual superintendents here and there have long been successful in giving vocational training to some of the patients under their care. This has been true especially in the training of tuberculosis nurses and laboratory technicians. Although it would be difficult to overemphasize the importance of giving patients a chance to study while they are curing it cannot be advanced as a solution of the difficult problems involved in the social care of the tuberculous. It is one phase of the solution, however, and no mean one.

Preparation for future jobs is in vain if there are no jobs or if they are remote in time or place. The establishing of social-service departments and case-conference committees, coöperation with placement bureaus and rehabilitation supervision are all necessary elements in a comprehensive plan of social adjustment There is, however, one important development which has gone on steadily for years with no fanfare of advertisement but which is probably the most significant movement in the field of the social treatment for the tuberculous group. This is the practice of employing ex-patients on staffs of sanatoria. Over 3,500 ex-patients are now employed in 60 different kinds of work in 294 sanatoria. The per cent of ex-patient employees ranges from 4 to 73 with a mean of 21 per cent. Since it is estimated that there are over 30,000 employment opportunities in sanatoria there is considerable chance for the growth of this procedure. Even at the present time there are seven times as many patients employed by the sanatoria as are employed in all the specialized after-care institutions and sheltered workshops for the tuberculous in the United States.

This problem of social diagnosis and social treatment (of the tuberculous) is so vast and it is so complicated with the numberless difficulties attendant upon prolonged illness that there is no touchstone of solution. Before any appreciable gain can be made, however, it must become generally recognized that the social symptoms of every case must be subjected to the same painstaking study as the physical symptoms. This is difficult and expensive. It requires a trained and skillful technique. But without such social care large sums of money will have been wasted and much skilled medical treatment will have been given in vain.

THE RELATIONS OF THE MAKE-UP OF THE BODY TO THE DISPOSITION TO TUBERCULOUS INFECTIONS AND THEIR COURSE[1]

LEWELLYS F. BARKER

Why do some persons remain free from any serious tuberculous disease throughout life whereas other persons manifest tuberculous processes of a greater or less degree of severity? Is tuberculosis commoner in some families than in others, and, if so, why? Are persons of certain types of physical make-up more predisposed to tuberculous disease than persons of other types of physical make-up? If there is a constitutional predisposition to tuberculosis, does this depend upon faults of "natural resistance" or upon defective acquisition of immunity? In how far is "constitution" dependent upon inheritance and in how far directly upon environment? These are questions that are constantly being asked, and in medical journals during past years many discussions bearing upon them have been published. From the standpoint of the history of medicine these discussions are of very great interest. For example, the term *habitus phthisicus* goes back to the time of Hippocrates. In my brief address it will not be possible to make any complete analysis of all the research work that has been done nor to deal with all the theories that have been propounded through the ages. I shall have to be content with giving you a general view of the situation as I see it and with a summary of the opinions that seem to me to be at the moment best substantiated by observation and experiment.

UPON WHAT DOES THE PHYSICAL MAKE-UP OF THE BODY DEPEND?

We know now from a long series of genetic studies that the development of the animal body (including the human body) depends upon two sets of factors: (1) those represented by the components of the genes of the chromosomes derived directly from the sperm-cell of a father and the ovum of the mother in the processes of reduction-division and fertilization (so-called "inherited or genotypic factors"), and (2) those repre-

[1] Address given by invitation to the Osler Club, Saranac Lake, New York, January 17, 1934.

sented by the substances that enter, and the various influences that act upon, the organism after its start as a fertilized egg-cell (so-called "environmental, paratypic or peristatic factors"). The whole development of the organism within the womb of the mother and in the world outside from the time of birth onward depends upon the reciprocal interrelations of these two sets of factors. It seems probable, too, that no two sperm-cells from any father and no two egg-cells from any mother are precisely alike in chromosomal structure; if this be true, it is evident that the organism that develops from any given fertilized egg-cell must be genotypically more or less unique, and that it ought not to be surprising if the sibs from the same parents should differ from one another to a certain extent, even if they were always subjected to precisely the same environmental influences, though, as a matter of fact, precisely identical environments, in turn, are never long experienced. One condition is, however, worthy of special mention, namely, that of "identical twins," which arise through a complete first subdivision of a fertilized egg-cell into two halves so that an organism develops from each half. These two organisms ought theoretically to contain precisely the same inheritance-factors, and, as we shall see, the study of identical twins has been made use of recently to throw light upon the problem referred to in the subject of my address.

WHAT DO WE MEAN BY THE TERM "CONSTITUTION?"

As each organism develops and continues to live, its genotypic or inherited factors are continuously interacting with environmental or paratypic factors to give rise to an ever-changing whole that is known as the "phenotype." It is not to be forgotten that, as development proceeds, the phenotype as a whole also reacts with its environment. Thus the genotypic factors within the phenotype are constantly interacting with paratypic factors of two sorts: (1) those already within the phenotype, and (2) those in the outside world.

A study of medical literature reveals a strange looseness in the use of the terms "constitution" and "constitutional factors," especially in relation to susceptibility to disease and resistance against disease. Thus, there are some writers who, when they speak of "constitutional factors," seem to mean inherited (genotypic) factors only, though the majority of authors appear to refer to factors of the whole bodily make-up, or phenotype (which is both genotypic and paratypic). The latter usage is certainly the more correct. It should be remembered, however, that some

think it wise to avoid making "constitution" and "phenotype" identical terms, agreeing with Diehl who defines "constitution" as a "relatively constant make-up of the body with regard to its resisting forces." These resisting forces can be changed by environmental influences that are strong enough to cause their permanent alteration or by influences that, though feebler, act upon the body at a time when it is for various reasons preternaturally susceptible to alteration.

RELATIONS OF "CONSTITUTION" TO "NATURAL RESISTANCE" AND TO "ACQUIRED RESISTANCE"

Much has been written about "natural resistance" and about "acquired immunity" to the occurrence of infectious diseases. Thus, all mammals other than man are immune from measles, a fact attributed to the existence of natural immunity as a "species" property. Again, within a given species there may be graded differences in natural resistance to diseases due to racial or to individual differences in constitution. The question then arises, Are these differences in "constitution" determined by heredity, by environment or by both? In some cases the answer may easily be given; thus, for example, avian tuberculosis does not occur in man apparently because man is protected by his body-temperature from its causative bacillus. It would seem probable therefore that "species" resistance is mainly, if not wholly, determined by factors of heredity. But, in other cases, especially when there are individual variations in resistance to a certain disease among individuals within a given species, the conditions are so complex as to make a decision regarding hereditary determination exceedingly difficult or impossible. Thus, for the occurrence and the course of human tuberculous disease, in which we are at the moment especially interested, the difficulties of decision are obvious; for, in addition to inborn resistance, we must give due consideration to degree of exposure and to the number of tubercle bacilli introduced, to the virulence of the bacilli, to preëxisting infections, to the conditions of climate and housing, and to the diets that affect nutrition. Is it any wonder then that there should be violent disputes as to the influences of factors that are hereditarily determined as compared with the influences that are environmentally determined in connection with tuberculous disease? What Lawrason Brown and his associates said in 1919 would seem to be as true to-day as ever; "The etiology of tuberculosis is not a closed book but one that contains many disconcerting and confused pages that need to be re-written."

During the past century, opinions upon the significance of the constitution for the occurrence of tuberculosis and for consideration in efforts at combating tuberculosis have passed through three or four stages. Before and after the middle of the nineteenth century (up to the time of the discovery of the tubercle bacillus by Robert Koch in 1882) chronic tuberculosis was regarded as a general disease of the body to be treated by general methods that increase bodily resistance. When Brehmer in 1857 wrote his dissertation on the curability of pulmonary tuberculosis, he believed thoroughly that the cause of the disease lay in certain definite anomalies of constitution which were manifested in the form of increased size of the lungs, small size of the heart and a narrowed vascular system. These anomalies that predisposed to phthisis were either inherited or acquired under the influence of chronic nutritional disturbances or other injuries of environmental origin. Accordingly, in the treatment of tuberculosis, these bodily inferiorities were to be overcome, and Brehmer tried to accomplish this by improving the bodily nutrition, by hardening processes, by systematic exercise of the bodily powers and by protection of the body from all forms of injury from without.

In a second stage, after the conviction that tuberculosis must be an infectious disease had grown, and especially after this conviction had been shown to be soundly based by Koch's discovery of the bacillus, the idea of a constitutional disposition to the disease was temporarily shoved into the background and medical efforts became predominantly centered in attempts to prevent the entrance of tubercle bacilli into human beings while infections that had already become established were to be treated by antibacillary measures. It became quite unpopular to speak of a constitutional disposition to tuberculosis, despite the efforts of a few to keep that idea alive. The orthodox bacteriologists of that time saw only the bacillus in aetiology and wished only to fight the bacillus directly when applying therapy!

In a third period, in which we now live, the effort is being made to evaluate properly both constitutional disposition and constitutional resistance on the one hand and the bacillary factor on the other. In no other way can the origin of the great variety of forms of tuberculous disease that occur in man be adequately understood. Even the specialists in bacteriology now recognize that the course of a tuberculous process in any given person depends in the main upon that person's natural constitutional mechanism of defense, even more than upon the alteration

that his constitution undergoes through the acquisition of a specific immunity after infection with the tubercle bacillus. Most will now agree that many children are born with a greater disposition to tuberculous infection than others and that also other children are born with a greater inherited resistance to that infection, or, in other words, both congenital disposition and congenital resistance to tuberculous diseases are now recognized.

It should be kept in mind, of course, that some diseases that were long regarded as hereditary in origin are not really so but are due to intrauterine infection from an infected mother. Thus the term "hereditary syphilis" is now known to be a misnomer since it has been shown that syphilis in the newborn is due to transfer of the *Treponema pallidum* from the mother to the child within the womb of the latter during the period of gestation. The question has been raised, "Does a tuberculous infection ever arise *in utero*?" Certain European investigators (notably Calmette and Valtis and Vandremer) have postulated the existence of an ultrafilterable form of tuberculosis virus, and maintain that there may be transplacental transmission of this ultravirus from mother to foetus. If this really ever occurs (and as yet it is doubtful) we should then be dealing with intrauterine infection, not with hereditary transmission.

ATTEMPTS TO MEASURE THE RELATIVE INFLUENCE OF HEREDITY FOR THE ORIGIN AND COURSE OF TUBERCULOUS DISEASE

Since it seems probable that both factors of heredity and factors of environment are concerned in the constitutional susceptibility to tuberculous infection and the resistance to tuberculous diseases, many attempts have been made to measure more accurately the relative importance of each.

Statistical genealogical studies have been made of single families and of groups of families. The method of "correlation" was applied by Pearson as early as 1912 to obtain direct evidence of the inheritance of a tuberculous "diathesis" and he believed that his results were positive though others are doubtful. Raymond Pearl, in 1920, reported his studies of the histories of families from the same economic and social strata for the incidence of clinically active tuberculosis and concluded that the genotypic factors of the constitution were not negligible, though, because of the great complexity and difficulty of the problem, he admitted that he could not bring absolute proof. Drolet (1924–1925) maintained that the children of tuberculous parents do not inherit a disposition to tuber-

culous disease but instead exhibit an increasing degree of immunity against it. Eberson (1928) laid stress upon the immunizing effect of primary infections with the tubercle bacillus, and thought that the relative immunity produced was partly antitoxic and partly antibacterial. O. T. Ryder insisted that the resistance offered in childhood on first encountering the tubercle bacillus must be an inherited trait, though he believed that the primary infection sensitized more than it protected.

Results of recent studies by the statistical method may be summarized in the statements that (1) bodily inferiority is not definitely demonstrable as a rule in the children of tuberculous parentage; (2) the course of tuberculous disease, when it occurs among children of tuberculous parentage, is not demonstrably less favorable than that among those of nontuberculous parents; (3) there are individual differences in susceptibility and resistance among members of families, some resisting the virus on strong exposure, others not doing so; and (4) in certain families there seems to be a site of diminished resistance (organ inferiority) to tuberculous disease (for instance, the right lung). But all agree that not too much reliance should be placed upon the results of statistical studies thus far made. The figures have been based largely upon anamnestic records (with the danger of too much mere "hear-say" evidence being included and without sufficient control by modern physical methods of examination or by X-ray studies).

During the past decade, the relation of inherited types of bodily make-up (*asthenic habitus*, *pyknic habitus*, etc.) to the incidence of tuberculous disease has been made the object of special research. The term "habitus phthisicus" of earlier times was applied to what we now designate the *asthenic* (or *leptosome*) *habitus*. Life-insurance data had long suggested that persons of asthenic habitus are more predisposed than other persons to tuberculous disease. And certainly, many practitioners of our own time have felt that a close relation exists between the asthenic habitus and susceptibility to tuberculous disease. It has been objected to this view that a great many Jews are of asthenic habitus though it is well known that members of this race are very resistant to tuberculosis, despite the fact that among them there are many who are poor. Possibly, as has been suggested, these leptosomic Jews have an increased immunity because of the fact that they live predominantly in towns and cities. As to persons of *pyknic habitus*, the impression is rather widespread among clinicians that tuberculous disease is relatively rare among

them. All these studies of the incidence of tuberculous disease in persons of different types of bodily make-up are strongly suggestive of the existence of inherited factors of susceptibility to tuberculosis, on the one hand, and of resistance to it, on the other; but the evidence is not yet fully convincing and a greater mass of material should be studied with as rigid control as possible of the data accumulated.

The strictest proof thus far of the relation of inherited factors to tuberculous disease would seem to lie in the studies that have been made of identical and nonidentical twins. Identical twins, as is well-known, resemble one another extremely closely because they develop from identical genotypic factors. The hair, the eyes, the skin, the tongue, the position and form of the teeth, the shape of the nose and of the lips, the ears, the facial expression in general, and the finger-prints, are alike. They are always of the same sex and their bloods belong to the same blood-groups. It is interesting that tuberculous disease of an organ (for instance, one kidney) may appear in identical twins in the same year of life (J. Bauer) and that the tuberculosis of such twins in general runs a similar course (D'Almeida), whereas in nonidentical twins there may be marked discordance with regard to tuberculosis (Curtins and Korkhaus).

About three years ago von Verscheuer and Diehl published the results of their systematic investigation of tuberculous twins and of twins that had lived in an environment in which they were markedly exposed to tuberculous infection. Through the coöperation of many physicians they were able to study some 75 pairs of twins, 23 pairs in the first decade of life, 25 pairs in their second decade, 16 pairs in their third decade, and 12 pairs between the ages of 40 and 60.

In 61 of the 75 pairs of twins it was possible to demonstrate the presence of either fresh or older tuberculous changes in the body. Only 14 pairs had been and were at the time of clinical and X-ray examination entirely free from evidences of tuberculous processes, though they had doubtless been infected soon after they were born, had lived in a tuberculous environment and had been exposed (some of them markedly) to repeated infection. Even though a brother, a sister, or several sibs had suffered from tuberculous disease or had died from it, those 14 pairs of twins remained healthy, a fact that von Verscheuer and Diehl regarded as important for the investigation of the relation between genotypic factors and resistance to tuberculosis. They feel sure that the essence of inherited disposition to tuberculous disease does not lie in nonspecific constitutional peculiarities but rather in a specific constitutional disposition to it; that is to say, one or more genotypic factors make their

bearer more likely than the average person to be nonresistant; absence of the same genotypic disposing factors will give a person a greater natural resistance to tuberculous infection.

HOW CONSTITUTION CAN BE CHANGED

Luckily, we can now do much to prevent and to cure tuberculous disease, not only by lessening exposure to infection but also by actually changing human constitutions. We cannot change the genotypic constitution but we can profoundly alter the paratypic constitution. Thus, if we combat disease-releasing or disease-favoring causes like undernutrition, lack of vitamines in the diet, insufficient exposure to sunlight and pure air, lack of regular exercise, occupational dangers, depressing psychic and social influences, and inadequate care during pregnancy or during convalescence from influenza and measles, we actually bring about important changes in the constitution that will increase resistance. Constitution is not a fixed unalterable entity; even when its genotypic components are bad we can do much by influencing its paratypic components. Therein would seem to lie our main hope for further progress in the conduct of antituberculosis campaigns.

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THE HEART AFTER PHRENIC-NERVE INTERRUPTION[1]

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In an effort to evaluate the effects of unilateral diaphragmatic paralysis by phrenic-nerve interruption, and the associated intrathoracic changes upon the heart, 100 successive cases have had physical, electrocardiographic and X-ray observations before and after this operation at Glen Lake Sanatorium for Tuberculosis. No other type of collapse therapy had been employed. Those with pleural effusion were discarded.

Attention is called to previous studies upon other series of pulmonary collapse from the same institution.

Series 1 (Hansen and King): 73 collapse procedures (pneumothorax, thoracoplasty and phrenic exairesis) in 66 cases. Almost invariably changes in QRS amplitude appeared after collapse, but were not related to the degree or direction of intrathoracic distortion.

Series 2 (Hansen and Maly): 57 cases of thoracoplasty. Changes in the QRS amplitude of the electrocardiogram developed in 63 per cent, considerably in degree in 23 per cent. The heart-position was definitely changed in 30 per cent (18 out of 57). Of all those showing electrocardiographic changes, including the slight ones, only one-third showed X-ray evidence of heart changes in the same direction.

Series 3 (Hansen and Maly): In 30 tuberculous patients without collapse therapy, studied as controls, changes in the electrocardiogram developed almost as frequently as in the collapse series, but showed a smaller percentage of marked changes. The difference was not marked enough to permit of conclusions.

MATERIAL AND METHODS

In the present series of 100 cases unilateral pulmonary collapse has been attained, partially or completely, by phrenic-nerve paralysis, in fifty-two on the left and in forty-eight on the right side. Physical, X-ray and electrocardiographic observations have been made before and after operation, and continued until the full effect of collapse had been

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obtained, and maximum fibrosis had taken place with its attendant intrathoracic deformities.

The height and direction of the QRS complexes in the electrocardiograms before and after operation were taken as the basis of grouping. Changes in P and T waves occurred infrequently and have been considered separately.

Four main groups were recognized, and later subdivided, as follows:

Group 1 (35) showed no change in QRS amplitude.
Group 2 (55) slight change.
Group 3 (8) moderate.
Group 4 (2) marked.

The heart position was determined by X-ray plates. It is to be noted that the electrocardiograms were taken with the patient reclining and X-ray plates with him in the upright position. Fluoroscopic observations, partly for the purpose of comparing the heart position in upright and reclining postures, were made on about a third of the series. No significant variations in heart position or change in posture were found and no reason for doubting the validity of the comparison between X-ray and electrocardiogram.

Group 1 (no change of QRS amplitude in electrocardiogram), 35 cases: Group 1 consisted of 35 cases without electrocardiographic change, although nineteen (54 per cent) showed demonstrable change in heart position. Of these eighteen were right-sided and seventeen left-sided, with nine right and ten left showing X-ray evidence of change in position.

Group 2 (slight changes in QRS amplitude after operation), 55 cases: Fifty-five cases showed slight changes in the electrocardiograms and, of these, forty-two showed demonstrable change of heart position by X-ray examination.

There were 27 right-sided operations and 28 left. In the right-sided 18 hearts were displaced toward the left or transversely and four toward the right or vertically. In one the electrical axis, as evidenced by the electrocardiogram, was shifted in the same direction and in eight in the opposite.

After left-sided operation 9 hearts were displaced toward the left or transversely, and eleven toward the right or vertically. In 8 cases the electrocardiogram showed a shift of the electrical axis in the same and in twelve in the opposite direction.

Group 3 (moderate changes in QRS amplitude after operation), 8 cases: Eight cases, consisting of two right- and six left-sided operations showed evidence of moderate electrocardiographic shift of axis. In 6 cases the heart was displaced, in three transversely or toward the left (one right and two left phrenicotomies) and in three toward the right (all left-sided operations). Two of the 8 cases showed no change in the heart position,—one after a right and one after a left-sided operation. The

TABLE 1

	GROUP 1	GROUP 2	GROUP 3	GROUP 4
Left-sided operations (52)	(17)	(28)	(6)	(1)
Heart displaced right	6	11	3	0
Heart displaced left	4	9	2	1
Unchanged	7	8	1	0
Group 5	—	19	4	1
Group 6	—	1	0	0
Indeterminate	—	8	2	0
X-ray and E.C.G. agree	—	8	1	1
X-ray and E.C.G. disagree	—	12	3	0
Indeterminate	—	8	2	0
Right-sided operations (48)	(18)	(27)	(2)	(1)
Heart displaced right	0	4	0	1
Heart displaced left	9	18	1	0
Unchanged	9	5	1	0
Group 5	—	1	0	0
Group 6	—	7	1	1
Indeterminate	—	19	1	0
X-ray and E.C.G. agree	—	0	0	1
X-ray and E.C.G. disagree	—	8	1	0
Indeterminate	—	19	1	0

electrocardiographic axis was shifted in the same direction as the heart position twice and in the opposite direction three times. In 3 cases the changes in QRS amplitude were moderate in degree, but not indicative of change in axis deviation. The heart had shifted slightly toward the left in one after right-sided operation, slightly toward the left in one, and moderately toward the right in two after left-sided operations.

Group 4 (marked changes in QRS amplitude), 8 cases: Only two cases, with a right- and one with a left-sided operation, showed marked elec-

trocardiographic change, and these were apparently consistent with the physical changes in direction. The one with a right phrenicotomy started with a normal electrocardiogram and heart position but developed a right-axis deviation with the postoperative retraction of the heart toward the right. The case with left-sided operation changed from a right-axis deviation with normal heart position to a normal electrocardiogram with a transverse heart position.

SHIFT OF AXIS DEVIATION

Comparing the preoperative tracings with the later ones, indications of a shift of the electrical axis toward the left, based on increase of R wave amplitude in the first lead associated with S wave increase in the third, were found in more or less degree in twenty-four of the patients, groups 2 to 4; and similar changes but converse in direction, indicative of a shift of the axis toward the right, were found in 10 cases. In most of the cases a single electrocardiogram would not have made the diagnosis because of the slight degree of abnormality, but a comparison of a series revealed that a shift had taken place and indicated the direction. Occasionally a series of tracings of the same patient in different degrees of collapse showed a progressive change. For convenience of analysis the cases showing a shift of the electrical axis toward the left have been designated as group 5 and those of the opposite direction group 6.

Group 5 (cases showing evidences of a shift of the electrical axis toward the left), 25 cases: In this group only one case had a right-sided operation, with only a slight change in the QRS wave-height, and the heart-position unchanged.

Twenty-four of this number had undergone left-sided operation. Six showed evidences of a right-axis deviation before operation. Four showed only slight deviation toward the left, one moderate and one marked. One had a left-axis deviation before operation, which later became more marked, and the rest of them, seventeen in number, had normal electrocardiograms as to axis deviation before operation, and later shifted toward the left; slightly only in 19 cases, moderately in four and markedly in one.

Ten times out of the twenty-four the heart-position was shifted toward the left, slightly in all but one and in that one moderately. In this case the heart had been in normal position before operation although the

electrocardiogram had indicated a right-axis deviation, later becoming a left-axis deviation. In 10 cases the heart had been definitely displaced toward the right after the left-sided operation, by the fibrosis attending the progress of the lesion in the lung, although the electrocardiogram indicated a shift toward the left. Four times the heart position was unchanged.

Group 6 (shift of electrical axis toward the right), 10 cases: Ten cases showed a deviation of the electrocardiogram toward the right, nine after right- and one after left-sided operation. In six out of the nine with deviation toward the right the heart was displaced toward the left, away from the side of operation, and in one toward the right or operated side. Two hearts remained unchanged in position.

The one case with electrocardiographic shift toward the right after a left-sided operation showed no heart change. In this group of ten only one was in agreement throughout, a right-sided operation, with a shift of electrical axis toward the right and a displacement of the heart toward the right.

THE T WAVE

Changes in the T-wave direction, size or shape occurred in 23 cases after operation, and involved either T1 or T2, alone or in combination, except once where a marked inversion of T3 alone occurred. In the cases with left-sided operation an increase of the T wave was seen five times, associated with change of the heart position toward the right in three; a decrease of T wave five times, with a displacement of the heart toward the right twice and toward the left once. Seven cases after right-sided operation were found to have increased the T-wave height, with shift of heart position toward the left five times; three had decrease of T wave,—two with shift of the heart toward the left. One marked increase of T3 and one abnormal T-wave contour appeared associated with shift of the heart toward the right. High take-off of T wave appeared in one case.

If T-wave uprightness is the normal, and a negativity or trend toward it indicates abnormality of myocardial function as seen in degenerative or toxic conditions of the heart, ten cases out of the twenty-three might be suspected of myocardial abnormality, because of development of T-wave negativity, or abnormal contour, while thirteen might be suspected of swerving away from abnormal trends because of increase of T-wave positivity in the significant leads.

As a matter of fact none of them gave any clinical indication of changes for better or worse. Fourteen of the T-wave changes occurred along with evidence of shift of electrical axis and fifteen along with X-ray evidence of heart displacement. Apparently in this group T-wave changes are unimportant and without diagnostic meaning.

THE P WAVE

Only six out of the 100 cases showed any changes in the P wave after operation, three an increase and three a decrease in amplitude. One patient had a tendency toward right-axis deviation, with a broad and exaggerated P wave in the first two leads, and an increase in these findings after operation. There was no X-ray or clinical evidence of mitral heart disease as was suggested by the electrocardiograms. In 3 cases the T and P waves were both involved concomitantly, showing one example each of increase and decrease of amplitude and one of inversion. The heart position changed only slightly or not at all in all these cases except one in which there was a moderate displacement toward the left after right-sided operation, and an increase of the P wave.

OTHER FINDINGS

No abnormalities of conduction or of rhythm occurred. In one case auricular fibrillation persisted without change during the entire period of observation and was apparently not related to the pulmonary condition. The average age of the patients is less than that when degenerative diseases are likely to appear. Many of them have, because of tuberculous disease, been forced to lead lives of comparative freedom from strain. This fact does not seem to account for the marked infrequency of rheumatic heart disease, however. The patients studied by us almost invariably have had healthy hearts, which have not seemed to suffer even after prolonged and at times extensive displacement by intrathoracic processes.

DISPLACEMENT OF HEART

The heart was displaced from its preoperative position 69 times, to a slight degree only in all but fifteen (fifty-four). After operations on the right side, thirty-seven in number, a preponderance of displacement toward the left, or transversely, occurred, twenty-nine shifting toward the left and only eight toward the right. This suggests a tendency for the collapse on the right side to push the heart away. Out of 32 cases with left-sided operations 15 hearts were displaced toward the left and seven-

teen toward the right, or healthy side. Postoperative changes caused a displacement of the heart toward the operated side in twenty-three of the sixty-nine, and toward the opposite side in forty-six, this tendency being especially marked in those with right-sided operations.

AGREEMENT BETWEEN X-RAY AND ELECTROCARDIOGRAM

If both X-ray and electrocardiogram indicate a shift of position and of electrical axis in the same direction, it has been considered in agreement, and, if in opposite direction, in disagreement. Only the changes occurring after operation have been analyzed, for not infrequently a retraction of the heart toward one side or the other would be accompanied by an electrocardiogram indicating a shift of the electrical axis toward the contrary side. Out of the sixty-five showing electrographic changes (groups 2, 3 and 4) eleven showed agreement, twenty-three disagreement and thirty-one gave indeterminate findings on the point. It is of interest to note that the two cases in group 4, with marked shift of electrical axis, were in harmony throughout. The right-sided operation was followed by a change from a normal electrocardiogram to one with a right-axis deviation, and by a retraction of the heart position towards the right. The left-sided operation was followed by a shift in the electrocardiogram from a right-axis deviation tracing to a normal one, and a distinct shift of the heart position toward the left.

SUMMARY

1. One hundred cases of pulmonary tuberculosis have been studied before and after the institution of unilateral diaphragmatic paralysis by phrenic-nerve interruption for the production of pulmonary collapse. Fifty-two operations were done on the left side and forty-eight on the right.

2. Electrocardiograms showed a change in the direction and amplitude of the QRS waves in sixty-five, slight in degree in all but ten (fifty-five), but enough to indicate a shift of the electrical axis toward the left in twenty-five (all but one after a left-sided operation), and toward the right in ten (all but one after a right-sided operation).

3. P waves changed only six times, and no evidence of auriculo-ventricular-conduction delay appeared.

4. T-wave changes appeared in 23 cases, ten times with an increased negativity in the significant leads, and thirteen with an increase of size or a decrease of negativity. No clinical or roentgenographic evidence of

myocardial changes appeared, or of defective conduction through the ventricles.

5. The heart position was displaced from its preoperative position in 69 cases. After right-sided operations there was a preponderance of shifting toward the left or healthy side (twenty-nine times out of thirty-seven). After left-sided operations the heart might be displaced to either side (fifteen toward the left and seventeen toward the right). Twice as many were displaced away from the collapsed side as toward it (forty-six and twenty-three).

6. Comparing the direction of the deviation of the electrical axis with that of heart displacement revealed agreement in eleven and disagreement in twenty-three.

7. No evidence of heart damage or disturbance of function appeared.

SOME PHYSIOPATHOLOGICAL ASPECTS OF ARTIFICIAL PNEUMOTHORAX[1]

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Since rest is considered a very important factor in the treatment of active and progressive pulmonary tuberculosis, there is a tendency to ascribe the beneficial results of artificial pneumothorax to the fact that it places the lung in partial rest. Experience has, however, proved that in most cases a moderately collapsed and functioning lung shows a better healing process than an extensively collapsed, nonfunctioning lung. It is apparent that, besides mechanical factors, some changes in the physiology of the lung must also be taken into consideration.

Before studying the physiological factors accompanying pneumothorax, it will be well to consider the physical laws governing the behavior of fluids accumulating in the pleural cavity (the term, fluid, is used as in physics, to indicate either liquid or gas).

PHYSICAL LAWS OF DISTRIBUTION OF AIR IN PNEUMOTHORAX

The distribution of pleural exudates has already received a satisfactory explanation. A review of this problem will therefore be of considerable help in our investigation.

In the beginning of the process, when the effusion is small, the exudate accumulates in the deepest part of the pleural cavity, the posterior costodiaphragmatic angle. This is, as should be expected, according to the law of gravity. Further accumulation of fluid proceeds in a peculiar way. The exudate occupies a space, separated from the lung by a curved surface, as this is indicated in the radiograph by a curved line. The highest point of this line is in the middle axillary line or scapular region, the line proceeding from this point downward and inward.

On physical examination this line can be easily mapped out. Between the spine and the curved line there is a space one to three inches wide, in which resonance and respiration are normal, but away from the curved line in a peripheral direction resonance is impaired and respiration is

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diminished. Thus, the space occupied by the exudate is of a conical shape, quite broad at the base and narrowing more and more toward the apex.

Ellis and Gurland in this country and Demoiseau in France have confirmed by experiments on animals the tendency of liquids accumulated in the pleural cavity to form a curved line, such as we have described.

Sahli was the first to explain the specific shape of this outline by elasticity of the lung tissue (1).

It must be remembered that the lung is least elastic at the root and most elastic away from it. The bulk of the collapsible tissue is at the base posteriorly. As suggested by Keith, the lung may be divided into three zones:

1: The root zone (bronchus, artery, vein, lymph nodes, fibrous tissue) is almost rigid.
2: The intermediate zone, in which vascular and bronchial ramifications radiate toward the surface of the lung with pulmonary tissue implanted between the rays. It is a zone containing structures of varying degree of extensibility and collapsibility.
3: The outer zone, from 25 to 30 mm. in depth, consists almost entirely of elastic tissue (2).

This distribution of collapsible elements in the lung explains why the periphery and the base collapse most and why the collapse decreases from the base upward. It explains, also, the conical shape of the fluid and the shape of the curved surface.

Now let us turn to the case of pneumothorax. Two facts must be clearly borne in mind:

First: Simultaneously with insufflation of the air into the pleural cavity, the lung by virtue of its elasticity recoils and a considerable space is left between it and the chest-wall. The insufflated air spreads in this space, becomes rarefied and under a lower pressure (negative) than the air in the air-passages of the lung.

Second: Since the air within the lung is of higher density than the air in the pleural cavity, a buoyant force will be transmitted through the alveoli by the air in the air-passages upon the gas in the pleural cavity. As a consequence, the air in the pleural cavity will be forced upward, and its bulk will accumulate at the apex of the lung (Archimedes's *Principle of Buoyance*). If only a small amount of air is insufflated, it will form a bubble at the highest accessible point. This is in perfect agreement with Emerson's experiment.

Emerson insufflated into the chest of a dog just dying, or just after death (in which case artificial respiration was employed), varying amounts of air, but always small amounts, less in volume than one lobe of the animal's lung. The animal was then frozen in the cold-storage chamber of the anatomical department. At the end of three days, at which time the dog was solid, the chest was opened and a cast of the air containing cavity was made with plaster of Paris. In each case Emerson found the air-chamber at the uppermost part of the chest: at the apex if the animal was hung head up; along the spine if left lying on the abdomen (3).

The same results are observed in our daily experience in pneumothorax treatment. Films taken after a few refills, when the amount of insufflated gas is still small, will demonstrate the air-bubble at the apex, provided there are no adhesions.

The shifting of the air-bubble to the uppermost parts explains an interesting phenomenon, observed in cases of a moderately collapsed lung free from adhesions and pleural effusions. If the patient quickly bends himself forward he feels his "heart and something else" turn and move toward the anterior surface of the chest. In fact, by placing one's hand on the patient's chest at the level of his breast and quickly bending him forward, one can feel an elastic body hit the hand. This phenomenon was first observed and described by Rist and Hirschfield (4).

Thus, experience and observation in pneumothorax both prove that air insufflated into the pleural cavity accumulates at the upper part, according to Archimedes's principle of buoyance.

After the insufflated air has accumulated at the apex and produced a certain amount of collapse, it will, with further insufflations, spread gradually downward, separating the lung from the chest-wall and causing further collapse. However, the amount of collapse decreases downward, since the air tends to crowd itself upward. After a moderate number of refills it will be noticed that a line similar to Ellis's curve separates the air-chamber from the lung. However, this line ascends from the peripheral middle part of the lung to the apex, and in that it differs from Ellis's effusion curve which descends from periphery to the base. The air-chamber is widest at the apex of the lung and gradually narrows to a point in a downward direction. As in exudates, the collapse increases from the hilum to the periphery. Obviously this curved line can be observed only in pneumothorax cases with a few adhesions or free from adhesions and when the lung is not too fibrotic.

If large amounts of air are insufflated, the upper parts of the pleural

cavity will become saturated with gas under comparatively high pressure. With further insufflations air will accumulate downward, compressing the base more and more.

Observation on effusions in the process of absorption show that the first parts to reëxpand are those closest to the mediastinum where there is only a thin layer of alveoli and, therefore, there is only a slight degree of collapse. The radiograph shows the dark shadow of the fluid gradually receding from the mediastinum toward the periphery. This can be best observed in hydropneumothorax cases. The last of the fluid is observed in the costodiaphragmatic angle, the lowest portion of the lung. In the case of pneumothorax, the absorbing process proceeds from the mediastinum to the periphery and from the lower parts upward, the last remnants of air being observed at the apex. This is again in agreement with the principle of buoyance.

A CRITIQUE OF THE THEORY OF SELECTIVE COLLAPSE

If the lung is involved in a morbid process, as tuberculosis, there is always a loss of elasticity and, consequently, of collapsibility of the extensible parts. Such a lung cannot be collapsed as easily as a normal one, and more pressure will be necessary to obtain even a moderate collapse. It must be remembered, however, that an inflamed organ can be easily damaged by pressure. Insufflations of 1000 cc. of air, as practised years ago, are usually followed by pain, dyspnoea, high temperature, increase of symptoms, and general toxaemia. It is believed now that moderate amounts of insufflated air on negative pressure serve the purpose of pneumothorax best. This procedure is only rarely followed by general and local reactions.

If a moderate pneumothorax on negative pressure is instituted in a case of far-advanced pulmonary tuberculosis with an apical or subclavicular lesion, the insufflated air will accumulate over the apex and produce a very satisfactory collapse with favorable results. The upper lobe, due to its own gravity and to the pressure of the insufflated air, will not only be separated from the chest-wall, but will even drop down to the first or second interspace. From the writer's standpoint, the satisfactory results of such a collapse are due to the fortunate location of the lesion at the point where the gas accumulates according to Archimedes's principle. Since lesions in far-advanced tuberculosis are usually located in the upper lobe, beneficial results of pneumothorax are observed frequently.

Splendid results of moderate pneumothorax were cited by numerous

authors, who, ignoring the principle of buoyance, advanced other theories to explain the beneficial results produced by insufflation of moderate amounts of air.

For instance, Morgan (5) believes that healthy parts expand freely, displacing the gas; the gas finds lodgment over the diseased parts, which, having lost their elastic properties, do not expand. Morgan interprets this phenomenon as selective collapse. But, as I mentioned above, the shifting of the gas is explained simply by Archimedes's principle of buoyance. Thus, the beneficial effects are due to the selective location of the lesion (at the apex or subclavicularly) and not to the selective collapse.

Gwerder (6), discussing the "low tension" pneumothorax, states that the air accumulates selectively over the diseased parts, since the "healthy parts cannot stand air" and displace it over the diseased parts. By "low tension" pneumothorax he apparently means moderate pneumothorax, with preservation of the function of the lung.

Bernou (7) differentiates between expansile pneumothorax and compression pneumothorax. He believes that in an expansile pneumothorax on negative pressure the diseased parts are collapsed the latest and therefore have considerably less tendency to reëxpansion. He explains it by development of fibrous tissue and gradual loss of elasticity. But, as it will be discussed later, the development of fibrous tissue is a late effect of the pneumothorax and cannot be a result of collapsing the diseased tissues. Bernou's technique is to give small amounts of air at short intervals, which is in fact very helpful in maintaining a moderate collapse with the preservation of the function of the lung.

De Martini (8), another believer in selective pneumothorax, admits that the real selective pneumothorax can be maintained in cases in which the involved upper lobe is free from adhesions or is tied only by a few adhesions while the base is firmly adherent. If De Martini would only take into consideration the principle of buoyance he would come to the conclusion that his selective collapse can be easily established by insufflation of moderate amounts of gas, disregarding the fact of whether the base is adherent or not.

Barlow (9) thoroughly discussed the question of selective collapse under partial pneumothorax. He believes that "his partial pneumothorax differs from the partial pneumothorax of the literature, because in his form it is deliberately prevented from becoming complete." Apparently Barlow deliberately gives moderate insufflations, maintaining a

moderate collapse. He believes that by giving moderate insufflations the air in the pleural cavity is free to be distributed according to physical laws. He does not state these physical laws, but concludes off-hand that the air may directly "produce a collapse of the most diseased region." If the diseased region, however, is located at the base, a partial pneumothorax will be of no avail, because the insufflated air will accumulate at the apex if the pneumothorax is moderate. The pneumothorax will be successful in a basal lesion, if the upper lobe is adherent and the lower lobe will be free from adhesions. In such a case air will accumulate toward the base, but again not on account of the selective pneumothorax, but on account of the selective location of the lesion and of the adhesions.

Barlow states that "only diseased lung tissue is compressed; healthy lobes being allowed to function nearly as before." However, in a regularly managed pneumothorax we don't try to compress: we try to collapse. Moreover, the healthy lung tissue collapses considerably easier than the tissue involved in a morbid process, such as tuberculosis. This can be easily demonstrated in cases free from tuberculosis, in which a pneumothorax was given by mistake or for diagnostic purpose. A healthy lung collapses to a great extent after a few refills. On the contrary, a lung involved in a tuberculous process is difficult to collapse.

All authors, advocating the theory of selective collapse, have made the mistake of assuming that the involved foci are compressed and that the air has a tendency to find lodgment over the diseased foci. They have ignored the simple principles of elasticity and buoyance. Undoubtedly, many of these authors knew that by their "partial or expansile" pneumothorax many complications (pleural effusions, displacement of the mediastinum with dyspnoea, febrile and toxic reactions, pain, spontaneous pneumothorax) could be avoided. It is believed now that all these complications are avoided by moderate insufflations and by collapsing the healthy tissues which surround the diseased foci.

HYPERAEMIA IN THE COLLAPSED LUNG AS A HEALING FACTOR

In a moderately collapsed lung, as has been already discussed, the healthy tissues around the diseased foci are the only ones which are collapsed. What then causes the beneficial effects of the pneumothorax? They cannot be attributed entirely to rest, since we do not produce an extensive collapse and always try to preserve the function of the lung. Apparently, other factors must be responsible for the effective and often rapid therapeutic results. These factors must depend upon the change

in the functions of the lung, and primarily, upon change in the small circulation.

Brauer and his associates believe that in a collapsed lung anaemia is produced and is accompanied by lymphstasis; to this they attribute the healing process. Bruns (10) concludes that the manner in which collapse is produced makes no difference: the same results are observed in atelectasis from pneumothorax, pleural effusions, pleural thickening and bronchial occlusion. He attributes the diminished circulation to an increased vascular resistance and also to a possible vasoconstrictor effect.

Another associate of Brauer, Le Blanc, produced a very interesting experiment. In a dog he clogged the primary bronchus and observed the oxygen content of the blood before and after occlusion of the bronchus. Making due allowance for the increase in cardiac work (rapid pulse), he came to the conclusion that the blood circulation of the clogged lung approached an anaemic condition, but did not appreciably vary from normal (11). However, by clogging the primary bronchus, Le Blanc produced considerably more than a moderate collapse. Most likely his experiment resulted in a massive collapse of the lung and therefore it cannot be taken into consideration.

Andrus instituted in an experimental animal, through ligation of the left primary bronchus, a collapse, with a 42 per cent decrease in the volume of the lung. The collapsed lung continued to transmit 30 per cent of the calculated cardiac output. Thirty days later the lung became completely atelectatic and transmitted only 8 per cent of the calculated output (12).

Sauerbruch ascribes the favorable results of pneumothorax to hyperaemia in the collapsed lung. Cloetta has proved this theory by plethysmography of the lung, by chemical analysis of the blood, and by comparing the microscopic slides of collapsed and distended lungs (13).

Tarantola mentions in his autopsy reports that the capillaries in the newly developed fibrous tissue, around the caseous foci, are usually dilated and packed with blood. In the collapsed lung the hyperaemia was quite marked (14).

Corper, Simon, and Rensch injected intravenously suspensions of prussian-blue, scarlet-red and starch into rabbits shortly after pneumothorax was instituted. These suspensions were found uniformly distributed throughout the lungs immediately after injection and up to two hours afterward. The gradual disappearance of prussian-blue within that time occurred uniformly on both sides. They concluded from their

experiments that the circulation through the collapsed lung was not decreased (15).

Although complicated and contradictory, these experiments on the whole are suggestive of a hyperaemic condition of a collapsed lung. Apparently, in a moderate collapse the lung is hyperaemic; in an excessive collapse, approaching an atelectatic condition, the lung becomes more and more anaemic.

For more definite evidence, we turn to our clinical experience in hyperaemia and anaemia.

It is well known that every organ is hyperaemic during its activity and in processes of repair and healing. Hyperaemia, provoked by injury, often leads to the cure of this injury. We do not know of any lesion which heals and regenerates by anaemia: if a healing process is present it is always accompanied by hyperaemia.

Farre and Travers in 1815 and Lois in 1826 called attention to the frequent coincidence of phthisis and pulmonary stenosis, the former being caused by the pronounced anaemia of the lungs in pulmonary stenosis. Later observers noted the fatal course of pulmonary tuberculosis in pulmonary stenosis (16).

On the contrary, Rokitansky stated that heart diseases, especially mitral stenosis, accompanied by hyperaemia of the lung, offer immunity against tuberculosis. He also observed that in cases of distortion of the spine, pulmonary tuberculosis occurs very rarely (17). It is generally accepted that stasis in the lung is accompanied by a certain immunity to tuberculosis.

Cornet considered stasis hyperaemia of the lungs a very favorable element in the healing process. In his opinion, hyperaemia is responsible for neutralizing the products of the metabolism of the bacteria, for destruction of the bacteria, and for stimulation of the tissues to the formation of connective tissue, which encapsulates the diseased foci (18).

Bier treated tuberculous joints very successfully by applying a compression rubber bandage above the involved joints. Even on slight constriction he observed very favorable changes in the condition of the joint. He explained it by hyperaemia created in the involved area, as manifested by redness in color and feeling of heat. Clinicians who applied this method of treatment could observe that only moderate compression gave good results. If the compression is increased, pain, more inflammation, and other unfavorable results complicated the course of the disease.

Practically the same phenomena are observed in a moderately collapsed lung. The collapsible elements around the diseased foci correspond to the rubber bandage applied above the joint. Due to the collapse a change in circulation takes place, resulting in hyperaemia.

Tiegerstedt concluded from the results of his experiments that the pulmonary vessels become more spacious in the beginning of inspiration (19).

It is believed that there is no vasomotor apparatus in the small circulation. At the same time, the blood-pressure of the lesser circuit is comparatively low (eighteen) and there is very little of muscular activity to help the propulsion of the blood-stream. Therefore, the expansion of the pulmonary vessels in the beginning of inspiration must be of great importance for the pulmonary circulation. Since in pneumothorax there is always some impairment of the lung expansion, a retardation of the blood-stream accompanied by hyperaemia can be expected.

When we immobilize a patient with a pulmonary lesion for a longer period of time we are trying to reduce the expansion of his lung, in order to produce hyperaemia. In fact, immobilization of a patient with inadequate circulation may result in stasis pneumonia.

Whereas the beneficial and rapid results of pneumothorax observed in the beginning of the treatment are ascribed to hyperaemia and autoimmunization, the later stage of healing (walling up of diseased foci and contracting of the cavities) is attributed to fibrosis developed by prolonged stasis.

Under continued pneumothorax treatment, the developed connective tissue penetrates gradually into the lung parenchyma and replaces large parts of lung tissue. Cavities become surrounded by dense fibrous tissue, their walls are gradually contracted, the size of the antrum may be decreased to such an extent that it appears as a narrow slit.

The rapidity of the development of fibrosis suggests how long the pneumothorax can be kept up. If the lung is moderately collapsed and if refills are given not too often and not in excessive amounts, the development of fibrous tissue proceeds slowly; the healthy parts of the collapsed lung become emphysematous (compensatory emphysema) and surround the contracted, nonfunctioning tissues. When such a pneumothorax is discontinued and the air is absorbed from the pleural cavity, the lung has still preserved, to a certain extent, its ability to reëxpand, and to fill out the pleural cavity without retracting the mediastinum extensively. On the contrary, in an extensive pneumothorax

the whole lung is collapsed toward the mediastinum, fibrosis rapidly develops and penetrates even into the healthy parts. If the pneumothorax is discontinued, the lung, because of a loss of elasticity, cannot reëxpand; the voluminous contralateral lung displaces it to the chest-wall and this causes a considerable retraction of the mediastinal organs. The final results of such a pneumothorax are not very favorable because of an extensive loss of function.

As mentioned above, in a moderate collapse, reactions are seldom encountered. When the patient becomes ambulant or is engaged in a gainful occupation, then the avoidance of reactions in pneumothorax treatment is very important. Apparently, each appreciable amount of air insufflated into the pleural cavity produces some therapeutic effect; it is very important that this therapeutic effect should not manifest itself by any reactions (as fever, pain, dyspnoea). The patient should leave the pneumothorax room feeling as comfortable as before the refill. Small reactions, some discomfort after a refill, are often followed by more severe reactions, disabling the patient and throwing him back.

Thus, the course and final results of a therapeutic pneumothorax are considerably better if the lung is moderately collapsed.

MANOMETRIC READINGS

The advocates of selective collapse in their discussion of manometric readings refer to the equal pressure in the pleural cavity which in their opinion is instrumental in an accumulation of air over the diseased part. This opinion is disproved by many authors. Von Muralt states that the pressure in the pleural cavity increases downward and peripherally away from the hilum. He explains this by the fact that the posterior and lower parts of the lung present the thickest layer of elastic and collapsible elements.

Roth has found in dogs a 20 per cent difference in manometric readings at various levels of the pleural cavity. In his experiments on small animals (rabbits) the difference was as high as 100 per cent.

Dumarest believes that the patient's posture is responsible for the difference in manometric readings; the pressure becomes considerably higher, if the patient sits up on the table. Sella observed an appreciable rise of pressure (registered by the manometer) when the patient sat up during a refill with the pneumothorax needle in his pleural cavity (20). An exactly similar observation was made by the writer.

Sella also investigated the manometric readings in 20 pneumothorax

cases. He took the readings with the patient lying on his back, on his side and seated. In all cases the readings were less negative when the patient was seated. This difference in readings is apparently caused by displacement of large organs (such as the liver and the heart), by mobility of the diaphragm, and by excursions of the contralateral lung. If the diaphragm and mediastinum are fixed, the change of manometric readings is considerably less (21).

If, after a refill, the patient sits up too quickly, a severe fainting spell may occur on account of the rapid change in pressure in the pleural cavity.

The observations of operators on pneumothorax resulted in reconsideration of Donder's theory of negative pressure in the potential pleural space. Muralt, Brauer, Tendeloo, West and others do not believe that there exists a negative pressure in the pleural cavity. According to their opinion, the pleural membranes are held together by cohesion and surface tension (22). If the wall of the thorax is opened at any point so as to make communication with the outside air, or, if the wall of the lung is pierced so that air can communicate with the pleural cavity from the inside, then the lung shrinks in size at once. Muralt states from his experience that when a sufficient amount of air or anaesthetic fluid enters into the potential space, the sheets of the pleura separate, the forces of cohesion and surface tension cease to exist, the lung collapses to some extent and negative pressure is created in the pleural space. Brauer believes that negative pressure in the pleural cavity is a pneumothorax sign (23).

This point of view is of practical importance in the process of inducing a pneumothorax.

Let us assume that the operator's needle has penetrated between the two pleural sheets (not tied by adhesions), and that the amount of air which has entered through the needle is not sufficient to overcome the forces of cohesion. In this case manometric readings will not be obtained. Let us further assume that the needle inserted more deeply enters the lung parenchyma and perforates a few alveoli. The opening is blocked by the needle. The end of the needle rests in interstitial tissue and no air from the lung can enter the pleural space; therefore, the manometer is still silent. The operator concludes that there is no free pleural space and withdraws his needle. He makes another attempt in another interspace. At this time he inserts his needle not so deeply, nevertheless high negative readings are obtained at once. The X-ray shows after a few refills a free pleural space without adhesions.

This can be interpreted in only one way. After the operator on the first attempt withdrew his needle from the lung parenchyma, air entered from the opening into the pleural cavity and a spontaneous pneumothorax was created. The opening was small; therefore it was easily sealed and only a moderate amount of air entered from the lung into the pleural cavity. On the second attempt, as soon as the needle penetrated through the parietal pleura, negative manometric readings proved the existence of an already established pneumothorax.

This happens more often than is generally believed, and it is therefore advisable, after each futile attempt to induce a pneumothorax, to fluoroscope or X-ray the patient. Sometimes the operator will be satisfied to find that his attempt was not futile, that a pneumothorax (a spontaneous) is already established, that a free pleural space exists and there is no difficulty in continuing the pneumothorax.

On the other hand the same experience is indicative of the very serious complications, which can be encountered in the process of inducing a pneumothorax (air embolus, spontaneous pneumothorax with excessive pressure or pyopneumothorax).

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PULMONARY LESIONS EXPERIMENTALLY PRODUCED BY INTRATRACHEAL INTRODUCTION OF ALUMINUM OXIDE AND OF BOROSILICATE-GLASS[1,2]

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In a previous study on the effect of particulate material on the parenchyma of the lung, silica was found to produce lesions that were similar in form and cellular construction to the nodules typically produced in man by the inhalation of silicon dioxide in the dusty air of mines or factories. In the present study, particles of aluminum oxide, of the same size and number as those of silica previously used, were introduced in the same way as the particles of silica had been introduced, and into a similar series of rabbits.

Aluminum oxide was used because it is frequently found in nature combined with silica, and because its chemical properties are similar to those of silica. In discussions regarding the aetiology of silicosis, attention is paid to the possible part played by silicates. There seems to be sufficient evidence that these compounds may produce fibrous pneumonoconiosis although the effect is not constant for all silicates. As the second substance for study, we chose borosilicate-glass because it is an inert substance capable of division into very fine and sharp particles and is relatively insoluble. If its reaction with the tissues simulated that of silica, whether from the shape of its particles, or its chemical constitution, then a characteristic overgrowth of connective tissue would result in the formation of a nodule resembling the silicotic "pseudo-tubercle." It was hoped that the action of the two substances, aluminum oxide and borosilicate-glass, might provide evidence regarding the comparative importance of the mechanical and chemical factors involved in stimulation of the hyperplasia of connective tissue which is constantly found in silicosis.

In this report, we shall describe the lesions of the lung caused by the

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[2] Read at a session of the Pathological Section at the thirtieth annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, May 16, 1934.

two test substances when introduced through an intratracheal cannula, and shall compare them with those of equal age, previously described, when employing the same technique and using particulate silica as the aetiological agent.

Gardner and Cummings introduced 1 to 2 gm. of particles of aluminum oxide 1 to 3 micra in diameter, in from 5 to 7 intravenous injections into rabbits over a period of four and three-fourths months. Animals were killed at intervals in the following twenty-two months, and failed to show any gross evidence that the injections had brought about any pathological change. The particles of aluminum oxide were distributed throughout the various organs, phagocytosed by phagocytic mononuclear cells, and carried as intracellular crystals throughout the tissues.

The reactions differed in several ways from those observed when quartz crystals of equal size and number were similarly introduced. Fewer phagocytes were required to care for the elimination of aluminum oxide, because each cell ingested an excessive quantity of particles. These ingested particles were so crowded into the cell's cytoplasm as to obscure the structural characteristics of the cell. The phagocytosed particles failed to produce any injury to the cell containing them, and failed to induce any persisting inflammatory reaction in the affected tissue. There was no evidence of mononuclear proliferation or of stimulation of fibroblasts, and no evidence of overproduction of fibrous tissue. Aluminum oxide did not cause lesions similar to those induced by silicon dioxide.

Jones examined the lungs of men who had been engaged in different processes of the pottery industry, as well as the lungs of those who had been employed in collieries, and the lungs of asbestos workers and of workers in other dusty trades. He studied the mineral residues obtained from these silicotic lungs after the organic material had been removed. As a result of these investigations, he was forced to conclusions regarding the aetiology of silicosis differing from those hitherto accepted. He quoted the definition of silicosis accepted at the International Congress on Silicosis, that the disease is "a pathological condition of the lungs due to the inhalation of silicon dioxid" and that to produce this pathological condition, "silica must reach the lungs in a chemically uncombined state." Jones found, however, that most of the material examined by him was not uncombined silica but consisted of minerals in which silicon is combined with other elements to form silicates. Of these silicates, *sericite*, a hydrated silicate of aluminum and

potassium, was abundantly present not only in the mineral residues of the lungs he examined but also in the rocks and materials which gave rise to the inhaled dust. He showed that the bulk of the finest mineral particles in a silicotic lung consists of minute fibres of silicate minerals, chiefly sericite, and that those rocks which produce the most dangerous dusts are those which contain the higher percentages of sericite. He expressed the belief that the inhaled dust of South African quartz-bearing rock is extremely dangerous in its silicotic effect, because of the aggregates of minute acicular fibres of sericite, and that the inhaled dust of the rock of India, which contains more quartz, is innocent in its silicotic effect because it does not contain sericite.

Jones further wrote: "No quartz-bearing rocks investigated by this author are known to have given rise to silicosis-producing dust except those which also contain abundance of fibrous aggregates of sericite or of fibrous silicate materials, loosely held together and easily freed into the atmosphere when the rock is drilled and blasted."

For these reasons, he declared that the part played by the silicates was an important one in the causation of silicosis, although "the silicates cannot be regarded as a single group showing a uniform effect on the pulmonary tissues and producing the same results of disablement and death of those affected." Although Jones did not sponsor either the theory of solubility, of Gye and his associates, or the earlier mechanical theory of the production of silicosis, yet he repeatedly described the physical characteristics of sericite, which he believed makes deep pulmonary penetration possible and thus lends support to the mechanical theory.

In his summary, he wrote: "These investigations are not concerned with the pathological condition produced by the minerals in the lung. Whether they merely act as mechanical irritants causing the growth of fibrous tissue as advocated by some well-known authorities, or induce chemical changes, as maintained by certain eminent pathologists, is a question entirely beyond the province of the author." His conclusions provide the former school with evidence of the presence in the lungs of thousands of acicular fibres that presumably could act as mechanical irritants, and the latter school with evidence of the presence of silicate minerals less stable than quartz and which, because of their physical form, expose a far greater surface in proportion to their volume than do the more compact grains of quartz. Chemical reaction takes place on the surface of the particles, and more surface gives greater opportunity for reaction.

Riddell has investigated the question of the aetiology of silicosis, and the question of sericite as a causative agent of silicosis. As yet, he has been unable to produce convincing evidence that sericite is the cause of the fibrosis in silicosis. Higgins and I are now engaged in a similar investigation and have been unable to produce a lesion in any way comparable to that uniformly produced by the same technique when using silicon dioxide. The experiments must be continued before the aetiological importance of sericite can be definitely established.

Our experiments, using aluminum oxide and borosilicate, had been planned before the publication of either the article by Jones or of that by Gardner and Cummings. We hoped to determine the part played by aluminum oxide and a relatively insoluble silicate in the production of silicosis, and to compare the reactive state with that of silicon dioxide which, under similar experimental conditions, was known to produce typical silicotic lesions. With these substances, it was hoped we might also be able to develop further evidence regarding the mechanisms, whether chemical or mechanical, involved in the production of the fibrotic nodules of silicosis.

For each substance employed, a series of 20 rabbits was used, and after intratracheal injection they were killed at intervals of from one to two weeks, through a total period of five months. The duration of the shortest experiment was one week, and that of the longest, twenty weeks. Osterberg prepared the aluminum oxide and the borosilicate by grinding them in a ball mill until the particles of each were from 1 to 10 micra in diameter. The majority of the particles were less than 5 micra in size, which permitted of their ready phagocytosis by the histiocytes of the lung. A large proportion of the particles were so small that they exhibited brownian movement. Of the particulate material 12 mgm. was mixed with 3 cc. of water, and the suspension was introduced into the trachea of each animal. Further injections were not made in the course of the experiment. In making the injection, each animal was anaesthetized with amytal, placed on a frame, and so secured that the animal could be brought to an upright position. Before elevation, an intratracheal cannula was passed through the larynx and into the trachea to a point immediately proximal to the carina. Then the frame was raised and 3 cc. of the suspension was injected into the intratracheal tube and allowed to find its way into the bronchi and bronchioles. Deep breathing and coughing usually succeeded the injection, but the tube prevented escape of the test materials. As soon

as the animals recovered from the preliminary irritation, the tube was carefully withdrawn to prevent further paroxysms of coughing. When the animal was breathing quietly, it was placed again in a horizontal position, removed from the frame, and returned to its cage.

EXPERIMENTS OF ONE WEEK'S DURATION

Aluminum oxide: Unilateral or bilateral partial or complete atelectasis was the first effect produced by the suspension containing aluminum oxide. Inflammatory reactions immediately succeeded and were represented by exudation of serum into the alveoli and escape of erythrocytes and polymorphonuclear cells from the capillaries. These preliminary reactions disappeared promptly and were succeeded by very marked evidences of phagocytosis in which the alveolar phagocyte took the most prominent part. The polymorphonuclear cells did not seem to attract particles of aluminum oxide, and in only rare instances were particles seen in the cytoplasm of these cells. The cytoplasm of the alveolar phagocytes, however, was in every instance literally crowded with particles which appeared as dark yellow or brown crystals that did not require the use of polarized light for their identification. The phagocytic alveolar histiocytes appeared in various stages of desquamation. In some instances they were in their normal position in relation to the alveolar wall; in other instances, partly detached, and in still others, completely separated and lying free in the alveolar space. The processes employed by the lung in removal of irritants seemed to be proceeding with great activity. Phagocytic cells were found crowded together in alveoli, alveolar ducts, bronchioles, and all of the finer and larger bronchi where the exudate was made up of leucocytes, erythrocytes, and these phagocytic cells. Phagocytic cells were not discovered in the process of penetrating the mucosa of the bronchi. Sometimes, polymorphonuclear cells had insinuated themselves between the epithelial cells of the bronchial mucosa but they did not carry any of the particulate material into the bronchial lumen. It is presumed that the irritating substances were being excluded by way of the bronchial tree and were being carried out by the force of expiratory expression, by cilia, and by the act of coughing. The activity of the processes of exclusion was not confined to one mechanism of removal. It was apparent that cells bearing particles were passing out of the lung by way of the lymphatic vessels. Those cells that had not been removed were always grouped in situations where lymphatic tissue is known to

exist. Such collections of phagocytic histiocytes appeared in the subpleural, the perivascular, and the peribronchial regions. They were crowded together, making irregular spherical aggregations which appeared grossly as cream-colored, miliary bodies rising above the surface of the pleura and above the cut-surface of the pulmonary parenchyma. The lesions were loosely constructed, without definite marginal limitations, and without any evidence of fibrotic investment. They were composed solely of mononuclear cells and there was no evidence of local hyperplasia of connective-tissue cells or of the purposeful concentric cellular arrangement found in the nodule produced in the same time by silicon dioxide. It appeared that the cells had been carried to the three situations, and there had filled up all the adjacent parenchymal tissue, so that the lesions were composed of conglomerate groupings of cells which had a size and form determined by the alveolar spaces and their alveolar walls. Very little inflammatory reaction was produced in the surrounding parenchyma and the cells were not destroyed by the ingested crystals. The very looseness in the construction of the involved portions of the parenchyma, and the absence of inflammation, indicated clearly that some factor was lacking which might create hyperplasia of connective-tissue elements and a resulting fibrosis even remotely similar to that induced when silica rather than aluminum is the particulate irritant.

Borosilicate-glass: In experiments of duration equal to that of experiments with aluminum oxide, but in which borosilicate was injected into the bronchi, the lungs were grossly normal in appearance. The pleura was mottled, smooth, and glistening and there were no visible nodules on the surface. On palpation, certain parts of the pulmonary tissue were firm, and the thickening could be felt throughout the course of the main bronchus. On section of the lung, grayish lesions produced a mottled appearance which clearly distinguished them from the normal parenchyma. These lesions were roughly spherical in form, and firm to the touch. They were more confluent and of larger size at the hilum than at the periphery of the lobe. Small, miliary, discrete nodules were seen both in the subpleural regions and closely related to the smaller bronchi and blood-vessels.

Microscopically, the distribution of the lesions was precisely similar to that observed when other forms of particulate material were employed. In these experiments of brief duration, congestion and atelectasis of parenchymal tissue was conspicuous. The alveolar spaces were crowded

together and distorted, but contained serum, erythrocytes, leucocytes and mononuclear phagocytes. Even the polymorphonuclear cells were occasionally found to have ingested silicate particles. Marked activity of the mechanism of exclusion of irritants was manifest. All of the air-passages, from alveoli to bronchioles, and thence to large bronchi, contained an exudate composed in part of phagocytes packed to bursting with crystals. Excretion did not occur through the circulating blood. No phagocytic cells ever were identified within the lumen of a blood-vessel. Active excretion occurred by way of the lymphatics, as evidenced by deposit of the laden phagocytic cells in the lymph nodes of the hilum, and in the lymphatic tissue related to the bronchi and vessels. The largest of these loosely constructed groupings of residual phagocytic cells which simulate nodules were associated with the larger bronchi or were subpleural, and were situated near the hilum of the lung. Throughout the duration of this experiment, there was not the slightest evidence that the silicate employed produced any hyperplasia of connective tissue. As with the lesions found when aluminum oxide was used, so those induced by silicate were formed by the packing together of phagocytic cells within the normal pulmonary parenchyma, and resulting obliteration of the normal spaces by crowding. The presence of silicate did not excite any irritative reaction productive of hyperplasia in the connective tissue cells of the lung. Borosilicate-glass seemed to be as inert and harmless as graphite and excited no greater reaction.

EXPERIMENTS OF FROM TWO TO EIGHT WEEKS' DURATION

Aluminum oxide: In all experiments during this interval, the lesions discovered were distributed throughout the lung wherever lymphatic tissue was most abundant. The largest and most conglomerate lesions were related to the largest bronchi and vessels. The smaller and more discrete lesions were related to smaller bronchi and vessels, or to the subpleural region, and thus they occupied the periphery of the pulmonary parenchyma. All the lesions were visible as well as palpable, and were seen as cream-colored nodules rising above the pleural covering or the cut surface of the lung. Microscopically, the lesions were found to be produced by mononuclear pneumonitis, which was not characterized by dense consolidation. All evidence of congestion and of polymorphonuclear leucocytosis, had by this time disappeared. The smaller lesions were ill-defined, their borders were indefinite, and they were bounded by a region of mononuclear alveolitis. There was no evidence

that fibrosis was being stimulated for investment of the lesions. An active process of exclusion continued to function by way of the air-passages and the lymphatic vessels. Alveolar spaces contained one laden mononuclear phagocyte or more than one, and every bronchiole and bronchus, from the smallest to the largest, contained an exudate composed almost entirely of mononuclear histiocytes, crowded to bursting with phagocytosed crystals. It appeared probable that the phagocytic cells containing the particles were wandering about from one lymphatic depot to another on their way toward the hilum and the bronchial lymph nodes.

In the lesions themselves, there was no evidence that necrotic changes had occurred or that the phagocytes were being destroyed by the ingested material. Even the walls of the alveoli involved in the nodule remained intact, and the parenchymal structure was neither obliterated nor destroyed. The nodule was identified simply as an aggregation of phagocytic histiocytes tightly packed together within pulmonary parenchyma (figure 1).

As time passed, the slightest evidence that the lesions might be permanent or progressive failed to develop because there was total lack of evidence of activity of the fibroblasts to form a fibrous envelope, and no evidence at all of metamorphosis of the histiocytes into fibroblasts. These two processes were conspicuous and characteristic of the lesions produced by silica within the same period. With the passage of time, there was a definite decrease in the size and number of the lesions, and all gross evidence of pathological change had disappeared after two months.

Borosilicate-glass: During a period of time equal to that consumed by the experiments with aluminum oxide, the reaction to borosilicate was so similar to that described for aluminum oxide that only the dissimilarities require attention. In experiments of two weeks' duration, in which silicate was used, a generalized increase in reticulum was found in those areas where lesions existed, and in the adjacent parenchyma where the alveolar walls were thickened by the presence of a mononuclear alveolitis. The reticulin was not in heavy strands and had none of the staining characteristics of true collagen.

In experiments of three weeks' duration, denser and more fibrotic lesions were found beneath the pleura and scattered throughout the parenchyma. Subpleural lesions occasionally appeared as plaque-like nodules composed of mononculear phagocytes. These cells stained

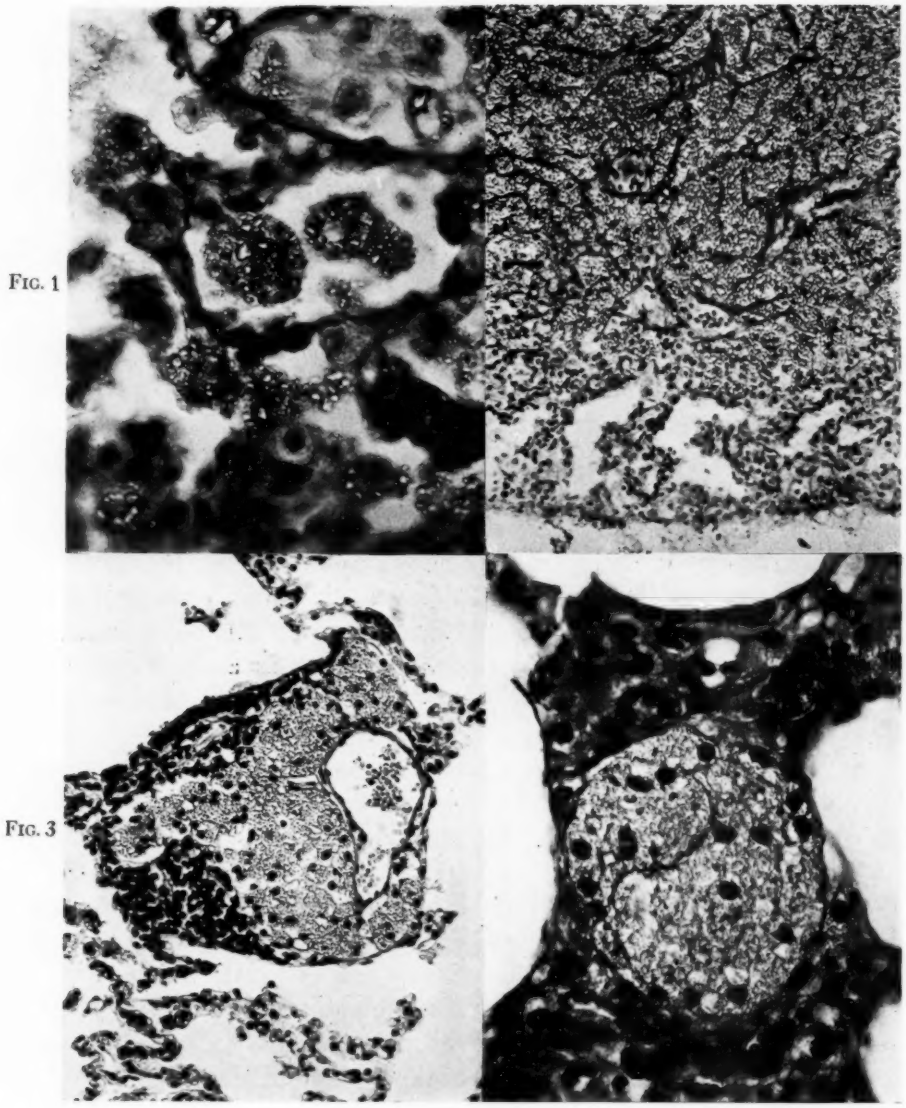

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 1. EXPERIMENTS OF FOUR WEEKS' DURATION

Histiocytes crowded with particles of aluminum oxide. The cells appear to be uninjured by ingested substances. There is no evidence of provocation of connective-tissue hyperplasia.

FIG. 2. EXPERIMENTS OF THREE WEEKS' DURATION

Subpleural nodules produced by crowding together of histiocytes packed with particles of silicate. Wisps of fibrous tissue divide the nodule into irregular parts. There is no evidence of the lamellar arrangement that simulates the pseudotubercle of silicosis.

FIG. 3. EXPERIMENTS OF FOUR MONTHS' DURATION

The lesion is related to one bronchus and one blood-vessel and consists of histiocytes crowded with ingested particles of silicate. Lymphocytic infiltration forms a boundary between the nodule and the normal pulmonary parenchyma.

FIG. 4. EXPERIMENTS OF FOUR MONTHS' DURATION

A small nodule found in a hyperplastic alveolar partition. The integrity of cells composing it is lost and only a few nuclei remain. Extracellular particles of silicate are packed together and the nodule is partitioned by a few fibrous bands. There is no lamellar arrangement or investing fibrosis.

faintly, but their cytoplasm was crowded with particles. They were packed together tightly, but without any specific type of arrangement. There was no evidence of central necrosis and no concentric peripheral fibrosis although fibroblasts appeared and formed fibrous strands which penetrated the lesions and divided them into cellular islands. In one instance, the lesion found at the hilum was devoid of any semblance of pulmonary tissue and the usual construction was entirely replaced by fibrous tissue. Giant cells were scattered among the fibroblasts, but there was no grouping suggestive of a nodule similar to that developed in silicosis. In experiments of five weeks' duration, the histiocytes showed the most remarkable capacity for phagocytosing particles of silicate. Cell protoplasm and cell outlines could not be distinguished because of the numbers of particles crowded within the cytoplasm. There was also an appearance, in some cases, that rupture of the cells had occurred and that particles had escaped and become extracellular.

By employing special stains for reticulin, it was found that wherever pneumonitis existed or histiocytes were grouped in nodules, there reticulin was increased in amount, and diffuse fibrosis was in process. The thickened reticulin occupied the situation of former alveolar walls, but it tended to broaden and encroach on alveolar spaces and to obliterate them. The parenchymal tissue, however, remained recognizable by the maintenance of its structural characteristics. The resulting fibrosis was diffuse, and without any of the concentric arrangement seen in the lesions caused by the reaction of the pulmonary tissues to silica (figure 2).

The production of fibrous tissue was stimulated by silicate more than by aluminum oxide, but borosilicate failed to produce an overgrowth of connective tissue resembling that found in nodules of fibrous tissue seen in man or in the silicosis of experimental animals.

EXPERIMENTS OF FROM EIGHT TO TWENTY WEEKS' DURATION

Aluminum oxide: Throughout this whole period, the lungs that were removed appeared, on gross examination, to be normal. Lesions could not be distinguished by inspection or palpation of the pleural surface, and the cut-surfaces of the lung appeared to be either perfectly normal or mottled in very small regions, in which the color was slightly more yellow than was the surrounding parenchyma. These lesions were distributed in the same areas as those found in experiments of shorter duration, and their size varied with the size of the vessel or bronchus that they approximated. Usually, the lesions were grouped about the larger

vessels and bronchi at the hilum of the lung. Microscopically, the lesions were made up of mononuclear cells which were so crowded together that they obscured the normal parenchyma of the lung. The cells were crowded with particles, and, in many instances, showed evidences of degeneration. Their outline could not easily be delineated, fragmentation had occurred and nuclear degeneration seemed to be progressing. Particles could be seen by the ordinary microscope, and, with the use of the oil-immersion lens, could be distinguished as being both intracellular and free within the lesions. Throughout this period, and especially toward the end of the third month, strands of fibrous tissue often passed from the periphery into the roughly spherical lesions and separated them into smaller cellular groupings. The fibroblasts failed to arrange themselves into a definite pattern, but proceeded irregularly throughout the lesion. Unlike the lesions of silicosis, these were not bounded by fibrous laminae, but, rather, the roughly spherical portions were poorly defined and without definite limitations separating them from the normal surrounding parenchyma. In certain sections, hyaline degeneration occurred adjacent to the lesions which had become almost entirely acellular. Invading fibrous tissue lost its staining qualities. Here and there, hyperplasia was evidenced by the presence of an occasional giant cell and a few mitotic figures.

No lesions could be discovered during the fourth and fifth months. However, an occasional histiocyte could be seen lying in the parenchyma, in which intracellular particles could be observed.

Borosilicate-glass: The arrangement of lesions and their gross appearance were similar to those produced by aluminum oxide and to those already described in reports of experiments of shorter duration. Differing from the latter, however, the lesions became fewer, much smaller, and much more difficult to distinguish on examination of the gross specimen (figures 3 and 4). As in the case of the lesions produced by aluminum oxide, there was a definite tendency toward grouping at the hilum rather than at the periphery of the lung. Microscopically, the involved areas were roughly spherical and indistinctly separated from the parenchyma; they were surrounded by a region of round-cell infiltration, but the immediately adjacent pulmonary parenchyma was entirely normal. When silicate was used, there was a greater tendency toward destruction of the phagocytic cell, but in many of the lesions the phagocyte maintained its integrity even though it was crowded to bursting with the particles. In no instance was there any evidence of necrosis, and

only rarely was a lesion seen in which there seemed to be any considerable degree of fibrous replacement. Small wisps of fibrous tissue often penetrated the lesion, apparently growing into it from the adjacent vessel or bronchus. Sometimes, the fibrous tissue formed bands that were broader and heavier, and more definitely marked out the nodule into smaller units. On using a special stain for reticulin and collagen, it was apparent that these substances were in larger amount than in the unaffected parenchyma. There was no suggestion that the histiocytes that formed the lesion were stimulated into division or into any transformation into fibroblasts, nor was there any indication that the fibroblasts were forming a protective investment encircling the lesion. When the tracheobronchial lymph nodes were examined, it was not unusual to see, even in these experiments of longer duration, that certain islands both in the central portion and at the periphery of the node were composed of histiocytes containing particles. In almost every instance, the histiocytes were grouped together and formed a miliary nodule lying at the periphery of the lymph follicle or distributed in the trabeculae.

SUMMARY AND CONCLUSIONS

Very fine particles of aluminum oxide and of borosilicate-glass, of a size permitting phagocytosis, were introduced through a tracheal cannula into the lungs of two series of rabbits, and the animals were permitted to live for from one to twenty weeks.

The particles of each material produced an immediate inflammatory reaction, characterized by escape into the pulmonary tissues of serum, erythrocytes, and polymorphonuclear cells. At the same time, phagocytosis of particles occurred, and the alveolar phagocyte was the most active and important phagocytic cell. Its efficiency as a phagocyte was evidenced by the very large numbers of ingested particles. These were often so closely massed, and so numerous, that they obscured the cytoplasmic detail of the cell, distorting the contour or rupturing the boundary of the cell.

Even in the experiments of shortest duration, there was evidence of migration of phagocytic cells, and of exclusion of them from the lung by way of the lymphatic structures and bronchi. The latter method of exclusion was indicated by the exudates containing phagocytic cells laden with crystals, in all of the divisions of the airway, from the alveoli themselves to the larger bronchi, the cilia of which were effective instruments in the process of removal. The former method of exclusion was

indicated by finding test material in the tracheobronchial lymph nodes, and by finding evidences of agglutination of phagocytes laden with crystals in all parts of the lung where lymphatic tissue abounds.

Throughout all the experiments, the lesions which appeared as miliary or confluent, roughly spherical nodules were found in the peribronchial, perivascular and subpleural lymphatic distributions. They were conglomerate and largest when situated at the hilum, and smallest and most discrete when related to smaller bronchi or vessels.

When aluminum oxide was used, neither the histiocytes nor the fibroblasts were stimulated to activity. The lesions were made up only of aggregations of phagocytic alveolar histiocytes, which gave no evidence of multiplication nor of transformation into fibroblasts. When borosilicate-glass was used, the lesions found after the longest period showed some evidence of replacement by diffuse fibrosis having taken place in the stroma of the lung. The earlier lesions were almost identical to those resulting from aluminum oxide.

There was no instance of a lesion, produced either by aluminum oxide or by borosilicate-glass, that even remotely resembled those produced by silica when particles of equal size, of uncombined silicon dioxide, were similarly introduced into the lungs of rabbits. There was no evidence that either material circulated in the blood-stream, and accumulation of phagocytic cells bearing crystals was not found in remote organs.

These observations seem to support the theory of solubility, of Gye and his associates, who have expressed the belief that the characteristic connective-tissue nodules of silica are produced because a tissue poison results from the contact of silica with the pulmonary tissues. Our experiments suggest that the biological activity of uncombined silica is absent when borosilicate-glass or aluminum oxide is employed and characteristic hyperplasia does not occur.

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SOME CLINICAL ASPECTS OF NONTUBERCULOUS ALLERGY IN TUBERCULOSIS[1]

JAMES E. SHERMAN AND ORVILLE E. EGBERT

The question of allergy in tuberculosis is of such scope as to necessitate a definite limitation of this broad field. Pinner (1) has discussed the relation between allergy and immunity in tuberculosis. His conclusions definitely preclude the possibility of allergy associated only with healing, as many patients with an allergic state will show healing and destructive processes in the same lung. An analysis of a great many cases of tuberculosis tends to reveal the rather pertinent fact that by far the greater number of tuberculous patients exhibit allergic phenomena when they are undergoing healing processes rather than when they exhibit symptoms of a retrograde condition, as manifested clinically and by laboratory methods of precision.

If we consider the classical example of desensitization of tuberculous guinea pigs (2) for the prevention of an anaphylactic reaction then the comprehension of allergic phenomena in tuberculous individuals is more easily grasped. Likewise, the desensitization with a small amount of horse-serum in a suspected allergic patient so that a larger amount may be safely given is comparable to the continuous desensitization that is always present in a tuberculous individual and accounts for the very fact that they can assimilate an enormous amount of toxin from active lesions and still live, by virtue of antibody formations, such as opsonins, antitoxins, agglutinins, etc. This in some measure explains the ability of patients who are very ill with tuberculosis to recover. An hypothesis presents itself concerning the ability of the so-called normal individuals to throw off tuberculosis when the opportunity presents itself, and we know also that this must happen often, as routine evidence of the disease from an X-ray viewpoint and from the tuberculin reaction shows the infection to be present in nearly all adults. This raises the question as to whether allergy and immunity are not synonymous. The point of view is more readily understood if we consider allergic phenomena a

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measure of immunity only in so far as its protective action is a result of physiological activity of the individual, without the anaphylactic reaction so dangerous to the patient. The allergic phenomena that we so often observe must, then, result in a supraallergic state which has gone beyond the stage of immunity.

An important fact should be inserted here, to be later explained, that the clinically observed allergy is always related to another foreign protein, not the one associated with immunity. Our criterion then for selecting demonstrable allergic conditions is that it must be primarily an anaphylactic phenomenon, generally manifested in many different methods. If we consider this condition as the assimilation of a foreign protein into the tissue cells in such a state that the cellular activity is impaired with resulting oedema (3) then the so-called allergic individual may exhibit his symptoms in numerous devious ways. Too, once a patient exhibits any of these phenomena his blood-plasma is so changed that he soon acquires other foreign proteins which acquisition may progress until the original inciting cause is lost in a maze of allergic symptoms.

Table 1 illustrates a few characteristic cases of allergy in tuberculosis. These cases were selected at random among those cases of phthisis that exhibit allergic phenomena of any type. Many more might be included, as, for example, the cases of asthmatic bronchitis, those of angina pectoris in individuals without evidences of arterial disease, and the many cases of intestinal disorders that are apparently caused by an offending protein. With the whole theory of allergy in such an embryonic stage, the absolute diagnosis of the aforesaid cases cannot be proved by postulation; therefore they are omitted, and hence no attempt is made to obtain the percentage of patients with tuberculosis that exhibit allergic phenomena. Attention is called to the numerous cases of pollen aetiology. This particular syndrome is not as prevalent in the sections of the country with a much higher humidity.

An analysis of table 1 is illuminating in several respects. One of the most significant is the fact that desensitization of these patients to their offending atopan does not influence the progress of the tuberculosis. The disease is neither better nor worse in terms of the X-ray, sedimentation records, monocytic-lymphocytic ratios, and clinical examination. This indicates one of two possibilities: (1) That allergy and immunity are not synonymous, as, while the allergic state is removed, the degree of immunity is not lessened, with consequent reactivation of the disease.

TABLE I

CASE	STATE OF TUBERCULOSIS	ALLERGY		EOSINOPHILIA	TREATMENT		STATE OF TUBERCULOSIS AFTER THERAPY
		Symptoms	Aetiology		Type	Results	
				per cent			
1. H. W.....	Arrested	Hay fever	Pollen	4.5	Desensitization (A)	Total relief	Arrested
2. W. C.....	Active	Asthma	Bacterial	5.0	Protein (B)	Partial	Active
3. T. S.....	Arrested	Asthma	Bacterial	3.5	Protein (B)	Worse	Arrested
4. C. C.....	Active	Hay fever	Pollen	—	Desensitization	No relief	Active
5. O. E.....	Active	Hay fever and migraine	Pollen, food	—	Food and elimination	Relief	Active
6. H. K.....	Arrested	Urticaria	Foods	1.0	Diet	Total relief	Arrested
7. R. W.....	Arrested	Asthma and migraine	Foods and bacteria	4.0	Refused	—	Arrested
8. M. M.....	Arrested	Hay fever	Pollens	1.5	Desensitization	Total relief	Arrested
9. C. C.....	Arrested	Hay fever	Pollens	2.0	Desensitization	Total relief	Arrested
10. W. V.....	Arrested	Hay fever	Pollens	1.0	Desensitization	Total relief	Arrested
11. M. H.....	Arrested	Hay fever	Pollens	3.5	Desensitization	Total relief	Arrested
12. C. B.....	Active	Asthma and urticaria	Bacterial and foods	6.0	Protein	Worse	Active
13. M. G.....	Active	Hay fever and migraine	Pollens and foods	—	Desensitization and diet	Partial relief	Active
14. Mc.....	Arrested	Lacrimation and asthma	Pyrethium	4.5	Removal of contact	Relief	Arrested
15. Fr.N.....	Active	Hay fever	Pollens	1.5	Desensitization	Partial relief	Active
16. W. O.....	Arrested	Asthma	Pollens	2.0	Desensitization	Total relief	Arrested
17. A. B.....	Arrested	Hay fever	Pollens	3.5	Desensitization	Total relief	Arrested
18. H. M.....	Arrested	Asthma	Bacterial	0.5	Protein	Partial relief	Arrested
19. W. M.....	Arrested	Asthma	Bacterial	5.5	Protein	Partial relief	Arrested
20. W. K.....	Arrested	Asthma	Hay fever, bacterial	5.0	Pollens, proteins	Partial relief	Arrested

(A): Desensitization with pollen extracts.

(B): Protein therapy includes both specific (autogenous vaccine) and nonspecific (peptone, milk, stock vaccine, etc.).

Due consideration must be given to the fact that the acquired allergy may not, and probably is not the original allergy that produces the tuberculin reaction. If we consider this fact then this first possibility, attacked from this angle, is not always true. (2) The second possibility is that a supraällergic state is present, so that when removed by desensitization the surplus allergic condition is ameliorated with resulting improvement. This too cannot influence the immunity of the case for, if allergy and immunity are synonymous, and the symptoms of allergy are manifestations of overimmunization, as in mild anaphylaxis, then when this overimmunization is neutralized the individual is no longer allergic and still has sufficient immunity to prevent the onset of an activation of the tuberculosis. One of these two hypotheses is correct: which one it is impossible to state at the present time. Tuberculin reactions are of no aid. One definite fact is outstanding, and that is that desensitization will not activate the progress of tuberculosis. This contention has been proved in guinea pigs and is now obvious in human beings.

Cases 3 and 12 exhibit another most interesting phenomenon. Cultures from the sputum were negative in intracutaneous tests. Likewise the filtrate would not produce a positive reaction. Complete food, pollen, contacts, and dust skin reactions were negative to both the cutaneous and intracutaneous methods of testing. The cases were thought to be a bacterial type with a filterable virus as the aetiological agent. Nonspecific protein therapy was attempted, using peptone, intracutaneously and subcutaneously. With each administration of the protein the allergic condition became worse although the state of their tuberculosis was unchanged. They were unable to tolerate a foreign protein, even though it was of the so-called nonspecific type. It is apparent then, that once a clinical allergic condition is present, it is entirely segregated from the tuberculosis. There is only one conclusion to be drawn, and it follows that the acquired allergy has nothing to do with the immunity of the individual. If the acquired allergy is the only allergic condition present in the individual (and it probably is not) an hypothesis might be drawn up that there is no relation between acquired allergy and immunity, which supports our previous contention. When we glance at the problem from a different angle and consider that the cause of the acquired allergy is a foreign protein ingestion in an already overimmunized individual and since the phenomenon of the acquired allergy is that of anaphylactic reaction we must recognize the existence of some preëxisting atopan which may or may not acquire a symbiotic protein and thus produce an allergic state.

Migraine is noticed as a persistent symptom in many allergic individuals. Hahn (4) believes, largely from Froelich and Meyer's deductions, that migraine is itself an allergic condition, and his views have been fairly well accepted in this country. However, pure migraine has not been encountered with tuberculosis. It does occur, and often, with other allergic phenomena, according to Hahn.

COMMENT

The above discussion is true of all types of allergy. The same problem is present in the desensitization of hay fever, urticaria or asthma. It is always a question of the discovery of an offending atopan. The question as to the relation of immunity and the original allergy that produces the tuberculin reaction is still open, but the evidence here collected and the conclusions drawn are all in favor of the two being synonymous. True, the acquired allergic state is not related to immunity, but neither is it related to the protein which is causing the immunity, or, in other words, to the beginning allergic state that is being gradually formed and produces the tuberculin reaction.

CONCLUSIONS

(1) Desensitization of a tuberculous individual to an offending protein is harmless, in that it does not incite an activation of the tuberculosis.

(2) The administration of the so-called nonspecific protein, in the ignorance of the existence of the inciting atopan, will sometimes cause activation of the allergy, but not of the tuberculosis.

(3) Acquired allergy is not related to immunity.

(4) Acquired allergy is most prevalent in arresting cases of tuberculosis, in which the immunity is greatest.

(5) The evidence so far gathered is in favor of the original conclusion that allergy and immunity in tuberculosis are one and the same.

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RIB-FRACTURE BY COUGH

Report of a Case

CARL R. HOWSON[1]

The possibility of rib-fracture by muscular action, particularly coughing, has been fairly generally recognized by the writers of books on surgery and fractures. Keene, Babcock, Robert and Kelly, Moorehead, Stimson and Kellogg mention it as occurring occasionally. Scudder makes no mention of it, nor does Lewis in his recent text. Lilienthal recognizes it, but I have been unable to find any reference to it in any book on diseases of the chest or tuberculosis.

The number of cases reported is not large. In 1917 Seilin (1) found the total of 51 cases in the literature, to which he added one. Since then, Webb and Gilbert (2) in 1923 reported three cases; Kleiner (3) in 1924 reported three and referred to an additional case in the French literature; and in 1929 Halliwell (4) reported the case of a physician with fracture of the 6th, 7th, 8th and 9th ribs along the posterior axillary line. His brings the total of reported cases to 58.

The patient was a young married woman, aged 26, with bilateral tuberculosis, very extensive on the left side. A thoracoplasty had been performed a few months previously, but her condition did not permit of the final stage before regeneration of the upper ribs occurred. She coughed very severely at times, and on several occasions during the previous few weeks had complained of pain low down in the right chest, aggravated by cough. She once complained of some similar pain on the left side. A tender ridge was palpable on the 10th rib on the right side, but it was thought to be probably an irritation at the costochondral articulation. At no time was crepitus demonstrable on either side.

Roentgenograms, taken about four weeks after the first complaint, showed a recent fracture of the 9th rib on the right side in the region of the anterior axillary line, a fracture of the 10th rib with callus-formation slightly further back, and a fracture of the 11th rib with callus-formation about the posterior axillary line. There was also a fracture of the left 10th rib about the mid-axillary line, with considerable callus-formation.

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I am in entire agreement with Webb and Gilbert (2) that these fractures are much more common than we have thought, and are undoubtedly frequently overlooked.

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INTESTINAL TUBERCULOSIS IN 1,400 AUTOPSIES[1]

PAUL M. CRAWFORD[2] AND HAROLD P. SAWYER[3]

In view of the variance of figures in the literature as to the incidence of tuberculous disease of the intestinal tract, it was thought that a survey of the material furnished by the first 1,400 autopsies at Fitzsimons General Hospital, Denver, Colorado, might be of interest as showing the frequency of this complication in a rather large series of cases of fatal phthisis.

Tuberculous enterocolitis is of interest to both the clinician and the pathologist because of its frequency as a complication of chronic tuberculous disease of the lungs and because of its profound influence on the prognosis of this disease. Brown and Sampson (1) remind us that it is the most frequent complication of chronic pulmonary tuberculosis, being found in 50 to 80 per cent of autopsies on individuals dead of the disease and having been diagnosed in 8 per cent of 1,801 consecutive admissions to the Trudeau Sanatorium. Williams (2) found intestinal tuberculosis in 81 per cent of autopsies performed at Brampton Hospital. Schwatt (3) reported an incidence of intestinal ulceration of 65.3 per cent in 199 autopsies. Rubin (4), at the same institution, reporting on 500 autopsies, found macroscopic evidence of tuberculous ulcers in 65 per cent. While there is less general agreement as to the relative frequency of laryngeal involvement, so frequently found in coexistence with enteritis in fatal cases, there is little doubt that the two conditions are the most usual complications of tuberculous pulmonary disease. It is known that intestinal involvement has the higher degree of incidence. Fishberg (5) states that the larynx is involved in about 45 per cent of fatal cases.

In a study of the material here reported it is scarcely to be expected that any new facts will be brought forth. Lawrason Brown (6) states that from 1893 to 1913 the articles written on tuberculosis required, for

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titles and reference alone, over 418 pages of fine print in the Index Catalogue of the Surgeon General's Library. However, in spite of important advances, particularly in the diagnosis and treatment of pulmonary tuberculosis, we have not advanced to a similar extent in the diagnosis or treatment of tuberculous enteritis, its most common complication. There is no general agreement as to the frequency of enteritis in nonfatal cases of pulmonary tuberculosis, and opinions as to its frequency in such cases, based upon a study of postmortem material, are open to question.

The statistics here given are from the first 1,400 autopsy protocols with their epicritical abstracts which were complete for the desired information. During the 13 years which they cover, 1921–1933 inclusive, accidents and repeated withdrawals from the files have caused total losses of some and disappearance of important parts of others. Even though some of the latter might have given valuable data they were not used. As the studies were made by each of us separately, one from the pathological (H. P. S.) and one from the clinical aspect (P. M. C.), a slight discrepancy of figures has resulted. This is observable in the total number of cases of intestinal tuberculosis and in the figures as to amyloid degeneration, and is due to the fact that a few cases reviewed pathologically were not suitable for clinical study. At the outset it will be well to emphasize that only ulcerative lesions are here considered. Whenever necessary, the differentiation has been by microscopic diagnosis; so the figures may be trusted for accuracy.

In these 1,400 autopsies, some form of tuberculosis occurred in 966 cases, or 69 per cent. Of these 966 cases, 950, or 67.8 per cent, showed pulmonary tuberculosis and only 16, or 1.2 per cent, were extrapulmonary. In this connection, it is interesting that no intestinal tuberculosis was found in these extrapulmonary cases.

INCIDENCE

The available figures in the literature of this subject vary from 8 to 90 per cent. This variance apparently depends upon the source of the figures, whether from pathological or clinical records, upon the type of lesion considered, and upon variations due to age, sex, and race.

In this series intestinal tuberculosis of all types occurs in 645 of the 966 cases of tuberculosis, or 66.8 per cent. Ulcerative intestinal lesions number 563, or 58.2 per cent.

Age is controlled, naturally, by the type of patients received at an

Army hospital, 17 years being the youngest recorded. No new or startling information is forthcoming, as is shown by table 1. As would be expected, the curve approximates closely that for tuberculosis and needs no comment.

TABLE 1

AGE	NUMBER OF CASES	PERCENTAGE OF INTESTINAL TUBERCULOSIS
17–19	7	1.2
20–24	92	16.3
25–29	138	24.5
30–34	149	26.5
35–39	104	18.5
40–44	36	6.4
45–49	22	4.0
50–76	15	2.6

Sex plays no part in these figures. While several female patients are recorded as having been autopsied, none had intestinal lesions.

Race is in the proportion of 462 whites to 101 negroes. This proportion shows nothing of value, since the admission of negro patients is controlled by arbitrary and extraneous factors. The interesting fact is, that of the 834 tuberculous whites 462 showed ulcerative lesions, or 55.4 per cent, while of the 116 tuberculous negroes 101 showed intestinal lesions, or 87 per cent. This greatly increased percentage in negroes may be almost wholly explained by the impossibility of inculcating habits of cleanliness and personal hygiene into these patients. Officers in charge of the colored wards find that sputum swallowing is universal and that emesis, which occurs frequently, brings up huge quantities of sputum and little else. The supposed higher susceptibility of the race is another factor.

LOCATION OF LESIONS

Combined lesions of both small and large intestines occur more than four times as often as lesions of the small or large intestines alone. Table 2 shows the figures with no need of explanation.

TABLE 2

LESION	NUMBER OF CASES	PERCENTAGE OF INTESTINAL TUBERCULOSIS	
Enterocolitis	315	55.9	69.7 per cent
Enterocolitis with appendicitis	77 (24.4 per cent of enterocolitis cases)	13.8	
Colitis	77	13.8	16.3 per cent
Colitis with appendicitis	15 (19.5 per cent of colitis cases)	2.5	
Enteritis	77	13.8	14.0 per cent
Enteritis with appendicitis	2 (2.6 per cent of enteritis cases)	0.2	
Appendicitis, total	94	16.7	

Comment, however, may be desirable. It is to be expected that the combined lesions should be numerically greater than lesions of either gut alone. The affinity of the tubercle bacillus for lymphatic structures almost ensures the involvement of both. It is probable, however, that enteric infection precedes colonic, both from location and from the predominance of lymph structures in the small gut. It is certain that spread to the *caput coli* must follow with little delay. All cases of enteritis alone exhibit the earliest forms of ulcers found. It is the experience at our autopsy table that, with only one or two exceptions, all preulcerative tubercles and beginning ulcerations are enteric. Only a few are colonic. Tuberculous appendicitis seems to be always ulcerative. There are no instances of preulcerative appendiceal tubercles in this series. Because of more limited accessibility, infection of the appendix must be more difficult than infection of the ileum or colon, but with greater certainty that the infections, once established, will flourish. Considering the number of intestinal infections it seems strange that, comparatively, so few involve the appendix. Only 16.7 per cent of all intestinal tuberculosis cases show tuberculous appendicitis.

TUBERCULOUS COMPLICATIONS OF INTESTINAL TUBERCULOSIS

Tuberculosis of other organs complicating ulcerative tuberculosis of the intestines occurs as follows (table 3):

TABLE 3

LOCATION OF LESION	NUMBER OF CASES	PERCENTAGE OF INTESTINAL TUBERCULOSIS
Larynx	206	36.6
Genitourinary tract	75	13.3
Liver and spleen	67	11.9
Liver, spleen and kidneys	55	9.8
Meninges	43	7.6
Liver	41	7.2
Kidneys	37	6.5
Spleen	30	5.3
Lymph nodes (caseous)	27	4.8
Liver, spleen, kidneys and adrenals	27	4.8
Liver and kidneys	15	2.7
Vertebrae	14	2.5
Spleen and kidneys	11	2.0
Adrenals	6	1.0
Kidneys and adrenals	5	0.9
Liver, kidneys and adrenals	4	0.7
Spleen and adrenals	4	0.7
Bones (various)	4	0.7
Liver and adrenals	1	0.2
Brain	1	0.2
Pancreas	1	0.2

It is not unexpected that the larynx leads the list. The fact that only a little more than one-third of ulcerative intestinal tuberculosis is complicated by tuberculous laryngitis is the matter for surprise. A less surprising figure is the corollary to this: namely, that, of the 213 cases of tuberculous laryngitis 206, or 96.7 per cent, showed intestinal tuberculosis. How the odd 7 escaped without infection somewhere in the intestinal tract seems the startling figure. Indeed, two of these seven were cases of preulcerative tubercles in the small intestine which we do not consider in this series. In these figures of the relation of intestinal tuberculosis to laryngeal tuberculosis there is no difference in percentage incidence between white and colored patients. Sputum swallowing seems to make no difference in cases in which saliva, food and drink are constantly dislodging fresh sources of infection from the open laryngeal lesions and depositing them at the door of the whole intestinal lymphatic system.

The remaining complications, in order of incidence, are of bare statistical interest only. These lesions are of all types and grades, from scattered minute miliary tubercles to massive caseation. The incidence

of the various combinations of organic tuberculosis reveals nothing extraordinary. They are of interest only from the point of view of the seats of election. Resolving these figures, we find the organs complicated in order of incidence as follows:

TABLE 4

Larynx	206	
Spleen	194	
Liver	169	
Kidneys	154	
Genitourinary	75	
Adrenals	47	
Meninges	43	
Lymph nodes	27	
Bones	18	(vertebrae 14, others 4)
Pancreas	1	
Brain	1	

PERFORATION AND PERITONITIS

Peritonitis occurs as a complication of intestinal tuberculosis 73 times, or 13 per cent. As might be expected, the majority, or 37, follow perforation of ulcers. More than one would expect, that is, 29, do not follow perforation but result from extension along the lymphatics and into the mesenteric lymph nodes, where softening and rupture of caseous tubercles into the peritoneal cavity evidently took place.

Perforation is multiple in 36 cases, single in one. The greater the amount of intestinal ulceration, the fewer the perforations found. The worst cases tend to hypertrophy and general fibrosis of the walls with apparent consequent strengthening of the ulcers. Most frequently the perforations occurs through moderately sized, rapidly advancing discrete ulcerations. In 3 instances such a rapidly burrowing ulcer had caused a slight local peritonitis which had glued its peritoneal surface to an adjacent coil of intestine with subsequent avulsion and tearing of the adhering base of the ulcer.

Peritonitis without intestinal ulceration occurs in 7 cases. These all were part and parcel of general haematogenous miliary tuberculosis. One was a most classical picture of peritoneal miliary involvement and would merit an illustration by itself, had not the economic depression wrecked our photographic department.

Two cases of perforation were found without any resulting peritonitis.

These occurred apparently just prior to death and time had not been given to disseminate the infection through the peritoneal cavity. Both deaths were due to haemorrhage.

TABLE 5

Amyloid

AMYLOID DEGENERATION			
With intestinal tuberculosis	95	Without intestinal tuberculosis	51
Liver, spleen, kidneys and adrenals...	40	Liver, spleen, kidneys and adrenals...	16
Liver, spleen and kidneys	13	Spleen	8
Spleen	12	Liver and spleen	6
Liver and spleen	8	Liver, spleen and adrenals	5
Liver, spleen and adrenals	7	Liver, spleen and kidneys	4
Spleen, kidneys and adrenals	4	Kidneys and adrenals	2
Spleen and kidneys	3	Spleen, kidneys and adrenals	2
Liver	3	Spleen and kidneys	2
Liver, kidneys and adrenals	1	Kidneys	2
Liver and kidneys	1	Liver and adrenals	1
Spleen and adrenals	1	Spleen and adrenals	1
Kidneys	1	Liver	1
Adrenals	1	Adrenals	1

Amyloid degeneration occurs in 146 cases of all forms of tuberculosis, or 15.1 per cent. It occurs in 95 of the 563 cases of intestinal ulceration, or 16.6 per cent. It occurs in 51 of the 403 cases of tuberculosis without intestinal ulceration, or 12.6 per cent. It occurs in 146 of the 1,400 cases reviewed, or 10.4 per cent. There is, therefore, but little difference in its incidence in this series. Since it is essentially a complication of tuberculosis and since tuberculosis forms so large a part of the illnesses in this hospital one would expect no great difference between its rate per tuberculosis cases and its rate per total autopsies. The factor of intestinal tuberculosis makes little change, for the percentages are 16.6 per cent for intestinal tuberculosis and 12.6 per cent for all other tuberculosis cases. Though the total cases are almost twice as many in intestinal tuberculosis (95 to 51), the number of cases of intestinal tuberculosis are much in excess of the cases of nonintestinal tuberculosis (563 to 403).

One fact brought out clearly in this connection is that when amyloid degeneration occurs at all it is far more likely to affect the spleen, liver, kidneys and adrenals together, than these organs singly or in smaller groups. Without going into any discussion of the mode of production

of this form of degeneration it would seem that these organs are its seats of election and that some blood-borne toxin causes fairly simultaneous change in the parenchyma of these organs, or the substance, elaborated in the circulating fluids, is deposited in them by preference.

The ulcers of intestinal tuberculosis are frequently enough seen to make description a needless bore. Moreover, this presentation lays no claim to be more than a statistical listing. Certain data as to type have been collected, however. First, it would appear that the classical girdling ulcer, which pursues its quiet and transverse way in the manner outlined for them by all authoritative text-books, is in the decided minority. Minute description has not always been found, but some reference has been made in the great majority of the protocols. It is surprising that of the 563 cases only 61, or 10.8 per cent, were mentioned as being of this type. On reviewing the 400 and some odd autopsies, which were performed by one of us (H.P.S.) in this hospital and in which care has been taken to mention these peculiarities, the percentage is about the same. Of course, some of these are early cases in which the ulcers have but just gained a foothold and have had no chance to begin their advance along the lymph-channels. Likewise, others have been stopped early by a wall of dominant resistance and have begun to heal. Nevertheless, the majority have been assorted lesions in all stages of advancement and should have shown more conformity to the established rules laid down by the ancient hierarchy of pathologists.

Unfortunately no definite figures for the entire series bear on the probable age of the ulcers found. The experience at the pathological conferences during the four years of our connection with this hospital may be categorically summarized in the statement that the great majority were evidently of more than six months' duration. This statement is based upon their size and general appearance, taken in conjunction with the details of the case history.

Local peritonitis over these ulcers is so frequent as to be the rule rather than the exception. It is mentioned in 79.2 per cent of the descriptions. These foci are usually small, extend a millimetre or so past the edges of the mucosal ulcer, are merely fibrinous or fibrous in type, and rarely form adhesions to adjacent structures except in the most advanced cases.

Eleven cases, 1.9 per cent, showed hyperplastic enterocolitis. These were all in the most severe types of ulceration and appeared to be the result of a long drawn-out disease, whose chronicity was the result of a

vigorous infection opposed by a less vigorous resistance. All were associated with varying degrees of peritonitis but without perforation, the peritonitis apparently due to involvement of the mesenteric lymph nodes, with softening and extension through the peritoneum.

Rapid advancement in intestinal ulceration frequently appears to accompany a satisfactory fibrosis and healing of the pulmonary lesion. The reverse of this is also true,—that a sudden flare-up of pulmonary virulence is associated with a beginning healing of the intestinal lesions.

One patient who died of pneumonococcic meningitis may be mentioned, in closing, for want of a better place and a satisfactory classification. This patient showed at autopsy 10 ulcers about 1 cm. in diameter, widely scattered through the intestinal tract. They resembled no other intestinal ulcers we have ever seen. They were very shallow, none extending entirely through the mucosa. They were smooth-edged and smooth-based, and showed no marginal or adjacent tubercles grossly. There was some focal peritonitic reaction. Some were healing. The case was neither clinically nor pathologically one of tuberculosis. Not another tuberculous lesion was found, either grossly or microscopically after the most painstaking search. Yet these ulcers were microscopically tuberculous, were surrounded by numerous marginal miliary tubercles and showed a plentiful supply of giant cells. The mechanism and source of this infection make interesting speculation. Cultures and smears showed the ordinary type of bacillus though it was thought that this might well have been an avian type through food infection.

CLINICAL SURVEY

Autopsy records showing ulcerative intestinal tuberculosis, or amyloid disease, as a complication of pulmonary tuberculosis, were studied with reference to the clinical features presented. It was thought advisable to exclude those of slight terminal intestinal involvement, as being of little clinical interest. After this was done there remained 560 cases which had findings of tuberculous enteritis, or amyloid disease, or both; 540 of these showed tuberculous enteritis at autopsy. From the clinical viewpoint the following points were considered of special interest:

1: Clinical course, with reference to the duration of the pulmonary symptoms, and also the duration of enteric symptoms.
2: Incidence of intestinal ulceration in cases arranged in groups on a basis of duration of pulmonary symptoms.
3: The degree of adequacy of the general treatment which had been carried out in these cases, so far as it could be ascertained from a study of the clinical histories filed with the autopsy records.

4: Use made of collapse therapy in the treatment of the pulmonary disease.
5: Treatment of the intestinal involvement.

It must be emphasized that this is entirely a study of postmortem findings, together with such clinical data as were available. Several pathologists and a considerably larger number of clinicians contributed to these records. In many instances the information available, from both clinician and pathologist, is quite complete. In others it is not as satisfactory as one might wish.

In considering the clinical course of the pulmonary disease, notation was made of the incidence of both enteritis and amyloid disease so far as possible in the various groups.

TABLE 6

Duration of pulmonary disease, with incidence of enteritis and amyloid disease

DURATION OF PULMONARY SYMPTOMS	NUMBER OF CASES	WITH ENTERITIS	WITH AMYLOID
Under 2 months	3	3	0
2 to 4 months	19	19	0
4 to 6 months	31	31	0
6 months to 1 year	121	119	4
1 to 3 years	173	171	24
3 to 5 years	45	45	14
Over 5 years	96	80	42
Duration unknown	72	72	6
Total	560	540	90

It is probable that these figures do not represent the entire incidence of amyloid disease in these cases, as in a number of the earlier cases Lugol's solution and microscopic sections were not routinely made. It will be noted that 290 cases, or 53.7 per cent, of the tuberculous enteritis occurred in the two groups whose pulmonary symptoms had a duration of six months to three years, as compared to 53 cases, or 9.8 per cent, in those marked by a fatal termination within six months of the onset of pulmonary symptoms. This finding supports the belief, generally held, that intestinal involvement is seldom a complication of acute phthisis. Amyloid disease, as might be expected, was limited almost entirely to those cases in which pulmonary symptoms had been in evidence for more than one year. It was chiefly dependent upon such factors as the amount of pulmonary cavitation, pyothorax, and abscesses in connection with tuberculous bone disease.

There were 510 cases in which it was possible to form a definite opinion as to the relative severity of the pulmonary and intestinal lesions. Of these, 343, or 67 per cent, showed pulmonary lesions which were considered severe in comparison to the amount of pathological involvement found in the intestinal tract. On the other hand, 56, or 10.9 per cent, showed a retrogressing enteritis of considerable severity, with a pulmonary condition apparently not sufficient to have been, in itself, a cause of death. There were 111 cases, or 21.7 per cent, in which an active and far-advanced pulmonary disease was complicated by a marked intestinal ulceration.

TABLE 7

Duration of enteric symptoms, with incidence of severe enteritis by groups

DURATION OF ENTERIC SYMPTOMS	NUMBER OF CASES	PERCENTAGE OF TOTAL	WITH SEVERE ENTERITIS	PERCENTAGE OF TOTAL
No symptoms	186	34.4	16	2.9
1 month or less	42	7.8	14	2.6
1 to 3 months	84	15.6	18	3.3
3 to 6 months	65	12.0	22	4.0
6 months to 1 year	58	10.8	20	3.7
Over 1 year	29	5.3	14	2.6
Unclassified	76	14.1		
Total	540	100.0	104	19.2

The duration of enteric symptoms was less than six months in 35 per cent of the 540 cases studied, while an almost equal group of 186 cases, or 34 per cent, were recorded as having had no definite symptoms of intestinal involvement. In this group are undoubtedly cases in which enteritis might have been diagnosed, or at least suspected, by close observation and critical evaluation of symptoms. Still, it is well recognized that there may be widespread intestinal involvement without symptoms or signs during life. Symptoms which were regarded by most of the clinical staff as indicating ulceration were diarrhoea, pain of a colicky nature and abdominal tenderness. Persistent diarrhoea usually indicated enteritis, amyloid disease of the intestine, or both. Dyspepsia, loss of weight, and constipation were usually considered insufficient for a diagnosis of intestinal ulceration. It will be noted that the enteritis cases with symptoms showed a combined incidence of severe enteritis of 16.2 per cent of the total of 540 cases, while the group reported as having had no symptoms showed 16 cases of severe enteritis, or 2.9 per cent.

It would appear that severe intestinal ulceration, while it may be asymptomatic, is not often so. It is noteworthy that in no case, showing at autopsy the preulcerative tubercles only, was there a record of any marked enteric symptoms. It is evident that pain is not caused until there is ulceration of the mucosa; it may not be present at any time, and it is a quite variable symptom. No definite relationship could be established between the location of the ulcers and the severity of the symptoms, or the predominance of any one symptom. Of more constant occurrence, particularly in late cases, is abdominal tenderness on palpation. Bruns (7) taught that it indicated deep ulceration with extensive involvement of the serous coat of the bowel, and that in patients who exhibited it a fatal termination was not far off. Of the 540 cases of tuberculous enteritis, 69.2 per cent either had no symptoms during life, or had symptoms for six months or less prior to fatal termination of the disease. This would seem to indicate that it is a late complication in a majority of cases. Schwatt (3) observed that in advanced phthisis the development of intestinal ulceration indicates *exitus* within six months. Amyloid disease was often missed clinically and, when recognized, was diagnosed on the existence of long-continued suppuration, an enlarged liver with firm border, or both. Diarrhoea seemed to be of no value in the diagnosis of amyloid disease, because of inability to exclude tuberculous enteritis.

The study of the adequacy of general treatment of these cases yielded little information. It was classified as good if there had been a reasonably early diagnosis of the pulmonary disease, if the patient had been hospitalized without much delay, if he had been treated by the best methods available at the time, and if he had coöperated in his treatment. Late diagnosis, delay in hospitalization, frequent interruption of hospital treatment by reason of the patient abandoning hospital, only to seek admission at a later date, drunkenness, frequent infraction of hospital rules, and other evidence of a failure to coöperate on the part of the patient, were considered evidence that the case had had poor treatment. Treatment which was considered good in 1921 might not be considered good in 1932. To-day collapse therapy must be used aggressively and early, as has been well stated by Peters (8). There were 279 cases, or 51.6 per cent, which were considered to have had good general treatment, and 199, or 36.8 per cent, in which the treatment had been poor. In 64 cases, or 11.8 per cent, the clinical history was not complete enough to permit this classification. It is evident that this

complication occurs in many well treated cases. However, as will be shown, in a majority of our cases collapse therapy was not used.

Notation was made of the use of collapse therapy in 95 cases, a total of 125 procedures having been carried out in these patients.

TABLE 8

Collapse therapy: 95 cases

TYPE OF COLLAPSE THERAPY	NUMBER OF CASES
Artificial pneumothorax	57
Phrenic exairesis	44
Thoracoplasty (including extrapleural pneumolysis)	24
Combined types	28
Artificial pneumothorax and phrenic exairesis (14)	
Phrenic exairesis and thoracoplasty (12)	
Artificial pneumothorax, phrenic exairesis and thoracoplasty (2)	

It should be noted that in 64 cases, or 11.8 per cent of the total of 540, the clinical history was missing or incomplete, so that collapse therapy was actually used on 95 of 476 cases, or 20 per cent. While thoracoplasty was always recorded in autopsy findings, there was none recorded in the 64 cases with incomplete clinical data. Artificial pneumothorax alone was used in 41 cases, and in combination with phrenic exairesis or thoracoplasty in 16 additional cases, a total of fifty-seven. Phrenic exairesis was used in 44 cases, alone in sixteen, with artificial pneumothorax in fourteen, with thoracoplasty in twelve. Thoracoplasty, or extrapleural pneumolysis, was used in 24 cases: alone in ten, with phrenic exairesis in twelve, and with phrenic exairesis and artificial pneumothorax in two cases. This does not represent the total of collapse therapy done in the 966 tuberculous cases coming to autopsy, since there were 403 without a complicating enteritis. This group was considered as outside the scope of this study and figures as to the treatment of cases in it are not available. In general, the use of collapse therapy has shown a steady increase since the earlier years of operation of this hospital. While there is no better way of preventing the distressing laryngeal and intestinal complications than by early and aggressive treatment of the pulmonary lesions, several factors apparently influenced adversely the use of collapse therapy in this group as a whole. In autopsy records of the first two years there is less evidence of pneumothorax than in later cases, and few thoracoplasties were done during this period. Through-

out the entire series many patients were terminal cases when first seen, and collapse therapy was not applicable. Finally, as in any large series of cases, a certain number refused any form of collapse therapy until the end was so near that the situation was hopeless. Still, the fact that 20 per cent of these cases had received some form of pulmonary compression compels the observation that tuberculous enteritis is not influenced in its course to any appreciable extent by compression of the diseased lung.

Treatment of the intestinal tuberculosis during the first five years (1920–1925) consisted mainly of bland diet, and intravenous injections of calcium chloride. In the past eight years, heliotherapy has also been used in a majority of cases. Codliver oil in tomato juice has been employed to a considerable extent in the past three years. In cases observed clinically during life, some amelioration of symptoms was occasionally noted, and appeared to be mainly due to heliotherapy.

Little information was obtained from our study as to the value of X-ray diagnosis of tuberculous enteritis, as this procedure had not been used routinely. It is of interest to note that there is still difference of opinion as to the value of this diagnostic aid. Fishberg (5) is not enthusiastic, stating that X-ray diagnosis was at variance with necropsy findings in 35 of 67 cases at Montefiore Hospital, while clinical diagnosis was 75 per cent accurate. In 12 cases of our series, 9 were correctly diagnosed by X-ray, and three were missed. In none of these 3 cases was there extensive ulceration of the intestinal tract. In 3 additional cases the diagnosis was made by removal at operation of a tuberculous appendix.

The following case is reported as illustrating the extent to which a complicating intestinal tuberculosis may dominate the clinical picture; it is also probably a case of unusually long duration of this condition.

P. A.: White, male, age 46, salesman, was admitted to Fitzsimons General Hospital May 10, 1929. History given was that in 1921 had noted onset of fatigue, cough, expectoration, fever, blood-streaked sputum, and loss of weight. A year later developed attacks of abdominal pain, nausea and pyrosis. Appendicectomy in 1923 followed by relief of abdominal symptoms for a year. In 1925 pulmonary symptoms again became troublesome; following sanatorium treatment in South Carolina pronounced an arrested case in 1927. In January, 1928, pulmonary symptoms returned, accompanied by abdominal pain and diarrhoea. During following year suffered severely from abdominal pain, diarrhoea of 8 to 20 stools daily, alternating with attacks of constipation. On admission abdomen very tender to palpation. X-ray of chest showed discrete caseofibrous lesions in upper half of left lung field only. No cavitation and

right lung was clear. A month later evidence of a cavity found in left lung, and artificial pneumothorax was begun. Almost simultaneously intestinal symptoms became much aggravated. On gastrointestinal X-ray series, followed by barium enema, in May and June, 1929, there was marked spastic hypermotility of caecum, ascending colon and first portion of transverse colon, and X-ray diagnosis was chronic tuberculous enterocolitis. It might be added that the X-ray evidence was hardly necessary for diagnosis. In spite of heliotherapy and intravenous calcium chloride, retrogression gradual and steady. In November, 1929, tuberculous laryngitis developed. Patient ran a fever of 102° to 103° each evening, developed fluid in left chest, and died January 5, 1930. Autopsy showed ulcerative largyngitis, and marked ulcerative enterocolitis from the jejunum to the ampulla of the rectum. The ulcers appeared older in the jejunum and upper ileum, more recent in the terminal ileum. The *caput coli* was one mass of ulcers and was thickened, indurated, and heavy. There was no amyloid. The lungs showed fibrous lesions throughout the left, with fibrosis of the right apex. There was 300 cc. of slightly cloudy fluid in the left pleural cavity.

SUMMARY

1. In this series, 68.8 per cent of cases of fatal phthisis showed at autopsy ulcerative tuberculous lesions of the intestines.

2. Ulcerative intestinal tuberculosis was found as a complication of tuberculous pulmonary disease in 87.5 per cent in the colored race, as against 42.2 per cent in whites.

3. Tuberculous laryngitis occurred in 36.6 per cent of cases of intestinal tuberculosis, but 96.6 per cent of cases of tuberculous laryngitis showed intestinal ulceration.

4. Only 10.8 per cent of the ulcers in this series were of the classical girdling type.

5. In 540 cases of intestinal tuberculosis complicating tuberculous pulmonary disease, 53.7 per cent occurred in cases whose pulmonary symptoms had a duration of six months to three years. In 34 per cent of cases the intestinal lesions were asymptomatic, and in 35 per cent the duration of enteric symptoms was less than six months. No cases, showing preulcerative lesions only, had marked intestinal symptoms.

6. There were 51.6 per cent of cases classified as having had good treatment, as against 36.8 per cent of cases showing evidence of serious deficiencies in treatment.

7. Some form of collapse therapy for the control of the pulmonary disease had been carried out in 20 per cent of the cases.

CONCLUSIONS

1. Intestinal tuberculous ulceration is found in a majority of cases of fatal phthisis.

2. The portal of entry for tuberculous intestinal infection appears to be the lower ileum.

3. In cases of fatal phthisis with intestinal ulceration the incidence of amyloid disease is only slightly higher than in those without this complication.

4. A large proportion of tuberculous intestinal ulceration is not characterized by any definite symptoms during life.

5. The clinical detection of late tuberculous enteritis is of prognostic importance only; it portends an early fatal termination of the case.

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THE PRECIPITIN TEST AS A MEANS OF DIAGNOSIS OF TUBERCULOSIS IN CATTLE[1, 2]

JANET McCARTER, WALTER WISNICKY AND E. G. HASTINGS

The purpose of this investigation was to ascertain whether the precipitin test could be used to supplement the tuberculin test for the diagnosis of tuberculosis in cattle. Such a laboratory test, supplementary to the field test, would be valuable, since the problem presented by the tuberculin-reacting animal, which shows no evidences of tuberculosis upon postmortem examination, continues to be one of significance in the tuberculosis eradication program of Wisconsin. The possibility that the precipitin test might be a more specific diagnostic agent than the tuberculin test was suggested by some work done for us by Seibert (1). She found that the serum from one cow which had been inoculated with a bovine strain of the tubercle bacillus gave a positive precipitin test with a much higher titre of antigen than did the sera from 10 no-lesion, tuberculin-reacting cattle.

TECHNIQUE

The blood samples for testing were removed from all tuberculin-reacting cattle by the field-workers, over a given period of time. The bloods were centrifugated and the sera examined for precipitins.

The antigen was prepared from an avirulent human strain of tubercle bacillus used in making tuberculin. The ultrafiltration method of Seibert (2) was used, according to which the tubercle bacilli are grown on a synthetic medium for three months, at the end of which time extensive autolysis has occurred. The cells are removed by a Berkefeld filter, and the filtrate concentrated by an ultrafilter prepared as described by Seibert (3). The protein solution is washed free from crystalloids with a one-half per cent phenol solution, and standardized by the method of Seibert (3).

[1] From the Department of Agricultural Bacteriology, University of Wisconsin, and the Division of Live Stock Sanitation, State Department of Agriculture and Markets, Madison, Wisconsin.

[2] Published with the permission of the Director of the Agricultural Experiment Station.

We introduced one modification in Seibert's method; namely, the use of Dorset's[3] (4) concentrated synthetic medium in place of Long's medium. The former medium was used because it appears to furnish a greater yield of protein per unit volume.

The testing of the sera for precipitins was performed exactly as described by Seibert (5). One-tenth cc. of various dilutions of the antigen with 0.8 per cent salt solution is layered with a capillary pipette over 0.1 cc. of undiluted serum in small tubes. The layered tubes are incubated at 37°C. for two hours and examined for rings. The tubes are then shaken, placed in the ice-box overnight, and examined for precipitate formation.

CONTROLS

The purity of our antigen was controlled by running duplicate precipitin tests on some of the cattle sera, using our antigen and a sample of Seibert's *TPA* antigen, with which she kindly supplied us. A sufficient number of such duplicate tests were run to assure us that our antigen gave results comparable to the *TPA* antigen.

Our antigen and our technique in general were also controlled by tests made on the sera of experimental animals. Precipitins were demonstrated, using our antigen, in the sera of rabbits and guinea pigs immunized with the same protein, and also in the sera of guinea pigs inoculated with a small dose of a virulent bovine tubercle bacillus. Seibert (5) also found that precipitins appeared in the blood of rabbits injected with the proteins of various strains of the tubercle bacillus and in the blood of tuberculous guinea pigs.

DATA

During the course of this study, 168 samples of blood were tested. The postmortem results on the animals from which the sera came were supplied by the Division of Livestock Sanitation of the State Department of Agriculture and Markets. A summary of the data obtained is presented in table 1.

	gms.		
[3]Asparagin	12.—	Magnesium sulphate	1.50 gm.
Dextrose	10.—	Ferric citrate	0.30 gm.
Di-potassium phosphate	1.50	Glycerine	100 — cc.
Sodium citrate	0.75	Water to	1,000 — cc.

TABLE 1

POSTMORTEM RESULTS	DISPOSITION	NUMBER OF ANIMALS	NUMBER OF ANIMALS SHOWING PRECIPITINS IN SERA
Lesions of tuberculosis:			
Slight, caseous or caseocalcareous lymph nodes	Food	99	3
Well-marked	Cooking	5	0
Extensive	Condemned	4	1
Skin lesions	Food	21	0
No visible lesions	Food	39	0

Further details of the serum test and of the lesions found are given in table 2 for the four animals in whose sera precipitins were demonstrated. A precipitate appearing with a dilution of the antigen of 1–10,000[4] or below was arbitrarily considered as a negative or nonspecific result, since our data showed that there was no correspondence between precipitates obtained at this dilution and the presence or absence of tuberculosis in the animal as shown by the postmortem results. As can be seen from table 2, there is apparently no relation between the extent of the tuberculous lesions and the presence of precipitins in the serum.

TABLE 2

REACTOR NUMBER	POSTMORTEM RESULTS	HIGHEST DILUTION OF ANTIGEN WITH WHICH A PRECIPITATE APPEARED	
		Ring	Precipitate
R16026	One slight caseocalcareous lesion	20,000	20,000
F94197	Slight, caseous lesions in bronchial and mediastinal lymph nodes	20,000	0
R49417	Slight, caseous lesions in bronchial and mediastinal lymph nodes	20,000	0
F94187	Extensive tuberculous lesions (condemned)	0	20,000

CONGLUTININ EFFECT

One serious difficulty was encountered in examining the bovine sera for precipitins which may have clouded some positive results. A precipitate appeared in some cases in the controls, that is, the serum + sterile 0.8 per cent salt solution. In reading these tests it was necessary to compare the degree of cloudiness and the amount of precipitate in the tubes

[4] One gram of protein per 10,000 cc. of physiological salt solution.

containing antigen with that in the control. This precipitate in the control was probably the so-called conglutinin effect which is due to the presence of some fibrinogen not coagulated during the clotting of the blood. Such simple procedures as recentrifugation of the sera or filtering them through paper failed to prevent the precipitation. Kyes and Porter (6) have found that the best method for obtaining fibrinogen-free sera of various animals is by precipitation with antifibrinogen sera from immunized rabbits, but this process would involve too much time to be of any practical value for our purposes.

DISCUSSION

It is evident from the data that precipitins were found in only a very small percentage of the sera examined. Over half of the cattle whose sera gave negative results showed as extensive lesions of tuberculosis as did those from which the positive sera came. This is in concordance with the results obtained by Seibert (5) in testing the sera of human tuberculous patients for precipitins. She found that only 6 of 51 samples of sera from these patients contained precipitins for the human tubercle-bacillus protein.

CONCLUSION

It seems clear from our data that the precipitin test is of no value as a supplement to the tuberculin test in reducing the ratio of no-lesion animals to the total number of reacting cattle.

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THE LYMANHURST CLASSIFICATION OF TUBERCULOSIS[1]

CHESTER A. STEWART, F. E. HARRINGTON AND J. A. MYERS

For some time a need has been felt at the Lymanhurst School for Tuberculous Children in Minneapolis for a practical and comprehensive classification that is applicable to all forms of tuberculosis diagnosed during life in children, and does not exclude that large group of cases with positive tuberculin reactions but normal X-ray films and negative physical and clinical findings. We have seen certain infected but otherwise negative children develop phthisis or some other reinfection form of tuberculosis later in life and are convinced that these patients who collectively comprise 75 per cent or more of the cases who are sensitive to tuberculin must not be disregarded in classifying tuberculous children. We also feel that, regardless of whether symptoms are present or absent, it is unsafe to make a clinical differentiation between cases with primary tuberculous disease and those with tuberculous infection if this distinction favors the assumption that patients classified as having a tuberculous infection but no tuberculous disease are protected to the extent that they enjoy a freedom from the danger of contracting some serious form of tuberculosis later in life, and thereby encourages dismissal from further follow-up supervision of the large group of infected X-ray-negative and symptom-free children. According to our experience it seems that regardless of whether symptoms are present or absent or whether primary tuberculous lesions are demonstrable or not, all infected children are faced alike with the common future possibility of developing some serious or fatal reinfection form of tuberculosis. Apparently the materialization of this possibility is so independent of the clinical manifestations and X-ray findings of primary tuberculosis that little or no certain prognostic significance can be attached to differentiating infected children from those who have primary tuberculous disease. We prefer, therefore, to classify all infected children with no demonstrable reinfection lesions as cases of primary tuberculosis, and to designate whether symptoms are present or absent mainly for the purpose of indicating whether or not active therapy (general care, and bed-rest) is deemed advisable.

[1] From the Lymanhurst School for Tuberculous Children, University of Minnesota, and the Department of Health, Minneapolis, Minnesota.

Several years of experience indicate to us that tuberculosis is essentially a biphasic disease in that two general fairly distinct but intimately related types of the disease occur in man, namely, primary tuberculosis (the first-infection type) and tuberculosis of super- or reinfection (the second-infection type).

In accordance with this concept, primary tuberculosis is defined as a general term or classification applicable to all cases with tuberculous lesions caused by a first infection of any part of the body with tubercle bacilli. In this large group are included all patients with positive cutaneous reactions to tuberculin and no demonstrable reinfection tuberculosis; regardless of whether the lesions of first infection are demonstrable during life or not or where they are located in the body. On the basis of X-ray findings these cases may be divided into a larger subgroup comprised of infected individuals with lesions that are not demonstrable roentgenographically and a second smaller group for patients with primary lesions some of which are visualized on X-ray films. Further subclassification of this second group with demonstrable foci of disease may be made whereby the location and gross appearance of visualized lesions comprising the primary complex is designated.

The following scheme presented here in outline form has proved satisfactory and practical for classifying all cases seen at Lymanhurst with primary tuberculosis and no demonstrable reinfection forms of the disease.

PRIMARY TUBERCULOSIS (THE FIRST-INFECTION TYPE)

In this general classification are placed all patients who are sensitive to tuberculin and who have no demonstrable reinfection type of tuberculosis. On the basis of X-ray examinations, this general class may be subdivided into the following two groups:

1: Primary tuberculosis; nondemonstrable

or

Primary tuberculosis with lesions that are not detected roentgenographically. (With or without clinical manifestations.)

(Since methods available for the discovery of tuberculous lesions of first infection during life are relatively crude the majority (75 per cent or more) of patients with positive tuberculin reactions must of necessity be placed in this composite group comprised of cases which include unidentified examples of intrathoracic, intra-abdominal, cervical or other forms of primary tuberculosis.)

2: Primary tuberculosis; demonstrable

or

Primary tuberculosis with lesions of first infection, some of which are demonstrable by X-ray examination. (With or without clinical manifestations.)

(A minority (25 per cent or less) fall into this group and may be subclassified as follows on the basis of visualized findings.)

A: Primary intrathoracic tuberculosis (The Childhood Type[2]).

1: With acute inflammatory lesions in the lungs and tracheobronchial lymph nodes.

2: With calcified or caseous parenchymal and lymph-node lesions.

3: With fibrotic intrathoracic lesions.

B: Primary intraäbdominal tuberculosis (with noncalcified or calcified retroperitoneal lymph nodes, with or without demonstrable tuberculous intestinal lesions).

C: Primary cervical tuberculosis (with noncalcified or calcified cervical lymph nodes, with or without demonstrable tuberculosis of tonsils, pharynx, nose and other portals of invasion).

D: Primary tuberculosis of other parts of the body.

In using the above classification one must remember that patients grouped separately on the basis of the location and appearance of certain lesions that happen to be visualized on the X-ray film may also harbor additional and important primary complexes in other regions of the body which escape detection. It also seems advisable to consider the large group in which infected patients are placed when their foci of primary disease cannot be detected during life as comprised of individuals who properly should be subclassified into various separate groups as cases with primary lesions in the thorax, abdomen or some other portion of the body, were it possible to demonstrate during life all foci of disease actually present. Since, however, patients with tuberculosis of first infection and no demonstrable reinfection form of the disease are fundamentally alike in many respects, the identification of individuals by tuberculin-testing who have been infected with tubercle bacilli is much more important than is the discovery of the location and appearance of some of the primary lesions known to exist. In other words, irrespective of partial information yielded by X-ray examinations relative to lesions of primary tuberculosis, it seems advisable to recognize that, as a group, patients who are sensitive to tuberculin harbor foci of primary tuberculous disease in which virulent bacilli may live for years; in general their

[2] As defined in *Diagnostic Standards*, issued by the National Tuberculosis Association.

normal immunological status has been complexly and lastingly altered, but in a manner which is fairly uniform throughout the group; their tissues react to the tubercle bacillus and its products differently than normal tissues do; they are sensitive in general to tuberculoprotein and collectively they comprise the group from which patients who develop various reinfection types of tuberculosis are recruited. The general fundamental similarity of patients with primary tuberculosis prohibits subdividing them into separate and distinct groups on the basis of whether one is able to detect lesions or not, unless the subgrouping is done without implying that cases placed in one class are basically different from those placed in another class or may be expected to show distinct group dissimilarities in the future with respect to freedom from or liability to the development of reinfection forms of tuberculosis. The classification is convenient, however, for indicating whether lesions present are discovered or not, and for describing them as well as for designating where they are located when detected, and must be used mainly for descriptive purposes.

As the result of several years of experience, we no longer make X-ray films of tuberculin-sensitive children primarily to discover lesions of tuberculosis of first infection. In such cases, we feel that only a few foci of disease actually present will be detected and that the undiscovered lesions are quite as important as are those which fortuitously happen to be visualized on the film. At the present time, therefore, we submit infected children to X-ray examinations of the chest mainly to exclude or discover pulmonary tuberculosis of the reinfection type (phthisis) which may be a public or individual health hazard and incidentally to demonstrate primary lesions and follow their evolution.

Tuberculosis of the super- or reinfection type is defined as a general classification applicable to all forms of tuberculosis caused by exogenous reinfection or endogenous dissemination of tubercle bacilli in patients whose bodies harbor foci of primary tuberculosis, and whose tissues were rendered sensitive thereby to tuberculoprotein. In this comprehensive classification are included various clinical types of tuberculosis such as pulmonary tuberculosis (phthisis), tuberculous meningitis, destructive tuberculosis of various other viscera, bone and joint tuberculosis, *et cetera*. In general, super- or reinfection types of tuberculosis differ markedly from primary tuberculosis to a degree that is surprising when their common aetiology is considered. The following classification for tuberculosis of reinfection is convenient.

TUBERCULOSIS OF SUPER- OR REINFECTION (THE SECOND-INFECTION TYPE)

1: Phthisis or the reinfection type of pulmonary tuberculosis (The Adult Type of Pulmonary Tuberculosis).

Exudative or Proliferative { (a) Minimal; (b) Moderately advanced; (c) Far advanced

2: Tuberculous pneumonia

3: Miliary tuberculosis

4: Reinfection tuberculosis of various other viscera

5: Bone-and-joint tuberculosis

6: Tuberculosis of serous membranes (meningitis, pleuritis, peritonitis, pericarditis).

7: Reinfection tuberculosis of the skin

8: Miscellaneous reinfection types of tuberculosis

It is to be remembered that patients with tuberculosis classed as super- or reinfection in character, also have primary tuberculous lesions somewhere in their bodies. These cases are placed in the reinfection group, however, in recognition of the fact that the form of the disease which they have developed postdating their primary infection is of major importance and overwhelmingly dominates the situation in so far as health and life and the need for therapy is concerned. The classification of tuberculosis presented here represents the most satisfactory method devised to date for classifying the cases studied during the past thirteen years at the Lymanhurst School for Tuberculous Children in Minneapolis and seems to be applicable to adults as well as to children.

DEFINITION OF PRIMARY AND SUPER- OR REINFECTION

Primary infection is defined as a term applying to single or multiple implantations of living virulent tubercle bacilli on tissues before they become sensitive to tuberculoprotein.

Super- or reinfection is defined as a term applying to single or multiple implantations of living virulent tubercle bacilli on tissues that are sensitive to tuberculoprotein. Such infections may be derived from exogenous and endogenous sources, and the development of sensitiveness to tuberculin establishes the dividing line which separates primary from secondary or superinfections.

PROBLEMS OF THE GENERAL PRACTITIONER IN TUBERCULOSIS

EDWIN J. SIMONS[1] AND JOHN B. SIMONS[1]

Since December 17, 1929, 30 cases of pulmonary tuberculosis have been encountered in a general practice centered about Swanville, Morrison County, Minnesota. Eighteen of these were discovered in the routine of practice; twelve, through efforts to trace the others epidemiologically. Various questions have arisen in this work, which are believed to be not peculiar to any one practice but to typify the difficulties of tuberculosis work in all general practices. The purpose of this paper is to discuss these problems in the hope that their elucidation will assist in the fight against the disease in rural districts.

Both the diagnosis and the treatment of the malady are fraught with obstacles and pitfalls for the rural physician. Diagnostic difficulties are undoubtedly of first importance. These may be divided into the problems presented by the atypical individual case, and those concerned with the epidemiology of the affliction. Questions of correct therapeusis for rural patients also must be given attention if the disease is to be adequately controlled.

Attention was first directed to the problem of diagnosis of tuberculosis by successive epidemics of measles and pertussis and the subsequent deaths of two patients from tuberculous meningitis. It became apparent that even the most detailed history and careful physical examination would not disclose every case of tuberculosis. In addition, repeated sputum examinations were made, basal-metabolism tests were performed when needed, and a daily temperature record with thermometer readings taken four times a day over a ten- to fourteen-day period was required.

However, it was not until the Mantoux and Pirquet tests were added to the diagnostic regimen that actual progress became noticeable. Each patient reacting positively to tuberculin has been subjected to roentgenographic study. All X-ray plates have been interpreted by either a

[1] Swanville, Minnesota.

roentgenologist or someone specializing in tuberculosis. These two phases of the diagnostic schema have furnished a solution for the problems presented by the individual atypical cases. Until the adoption of the use of tuberculin in diagnosis a sense of insecurity and inadequacy was unavoidable. After tuberculin was added to the diagnostic armamentarium many of the questionable cases were found unmistakably to be one form or another of tuberculosis.

Even cases which did not present symptoms or findings typical of pulmonary tuberculosis have been demonstrated to be of a tuberculous nature. Now all atypical cases of either adult or childhood pneumonia, all cases of sudden or unexplained elevation of temperature, of recurrent hoarseness, atypical hyperthyroidism, and doubtful pleurisy are subjected to either a Pirquet or a Mantoux test. That such a procedure is justified is attested by the resultant demonstration of tuberculosis in two cases of atypical childhood pneumonia, in two cases with recurrent hoarseness, one peculiar case of suspected hyperthyroidism, three cases of pleurisy, and one patient whose only complaints were tiredness and loss of weight. Now, through the use of these tests many cases with vague, indefinite symptoms and few or no physical signs either become tuberculosis-suspects or are pronounced nontuberculous. More general use of the tuberculin tests by general and rural practitioners will go far in solving diagnostic difficulties in rural districts.

In general practice outside the cities the epidemiology of tuberculosis constitutes a real problem, the solution of which is dependent upon the interest and coöperation of the rural physician. Here again tuberculin tests offer the first means of approach. Whenever an individual is found to be tuberculous through use of the diagnostic schedule previously given, every member of the patient's family is tested with tuberculin. After this is done other contacts from whom the patient may have become infected or to whom it may have been spread are tested. The family's milk supply is, when necessary and possible, subjected to tuberculin tests. Other possible sources of infection or channels of dissemination are also investigated. Thus, then, tuberculin-testing provides the first means of epidemiological diagnosis.

Although tuberculin is indispensable to the unfailing diagnosis of tuberculosis in rural districts, its use introduces one of the greatest dangers in recognition of the disease. This is involved in the interpretation of the roentgenogram. Each of the 30 cases cited has met the diagnostic requirements of the National Tuberculosis Association, yet

in only those instances in which tubercle bacilli have been found in the sputum or pleural fluid have local interpretations of the films been considered reliable. It is felt that only those general practitioners who have had special training in tuberculosis or in roentgenology should pass final judgment on films of persons suspected of the disease. This should not, however, imply any defects in the ability of the general practitioner. It is only too apparent that when some cases require serial plates taken over a period of many months before roentgenologists and specialists in the field of tuberculosis can make a definite diagnosis, the family doctor at one glance cannot be expected to diagnose the disease with dependable accuracy.

It is at this juncture that the rural physician encounters one of his greatest difficulties in connection with the problem. Strange as it may seem, the trouble is not merely medical, but financial as well, even though its influence strikes at the very ramparts of the rural conquest of the disease. The patient is reluctant to incur the expense of the Mantoux test and X-ray study, and when the doctor mentions the additional fee for interpretation, the patient often refuses to let the film be taken and also assumes that the local physician is culpably ignorant. Refusal to allow the roentgenological study occurs frequently enough when only one patient in a family is involved, to say nothing of instances where epidemiological investigation involves many more.

Perhaps a case will show the real proportions of this problem.

A man, 24 years old, presented himself, complaining of cough, thoracic pain, dyspnoea, fever and loss of appetite. On physical examination a pleural effusion was demonstrated and a roentgenogram confirmed this impression. Fluid was sent to the State Laboratories for examination and guinea-pig inoculation. The young man belonged to a family that included, besides himself, five other adults and five children. It was necessary to subject each of these to the Mantoux test, especially after the patient's reaction was found to be a grade-three positive. Eight other members of the family produced positive reactions and required roentgenograms. The family has always been quite comfortably situated financially; yet recent agricultural conditions have been such that the proper epidemiological studies could not have been done except at the bare cost. Consequently, for the eleven Mantoux tests and nine X-ray plates a charge of eight dollars was made, of which five dollars is to be paid for proper interpretation of the films. Three other members of the family had sufficiently suggestive findings to require later roentgen films. These three, if found to be tuberculous, could not have been correctly diagnosed without proper roentgenographic interpretation.

Other similar instances are numerous. At the recent state medical meeting another general practitioner stated that he had at last found a way to have his thoracic films interpreted at a small cost, and it is believed from other experiences that this problem is not peculiar to Swanville. It is not just to require that the general practitioner pay for such service out of his own pocketbook, and it is equally unjust to allow the roentgenologist or specialist in tuberculosis to render such service at a reduced price. In fairness to all concerned, this problem could be solved by the designation of some individual or institution by whom or where accurate interpretation of thoracic films of tuberculosis-suspects could be obtained without cost to the patient or rural practitioner. Since this would overcome one of the principal obstacles in correct diagnosis of tuberculosis in rural patients, the expense would be justified eventually by the advancement of the antituberculosis campaign which it would aid.

Therapeutic difficulties are less clearly defined. Still, proper management of cases found in rural practice would unquestionably reduce both the incidence of and mortality from the disease. Of the 30 cases noted, two died of tuberculous meningitis before or immediately after a pulmonary lesion was found. Thirteen of the remaining twenty-eight were sent to a sanatorium and the rest remained at home. Three of the sanatorium patients have died, including two 'teen-age girls and one patient 63 years old. All of these were far advanced when first seen and two died after leaving the sanatorium. All the other sanatorium patients have made satisfactory progress or have recovered sufficiently to resume their work.

Of the 15 cases cared for in the home, three have moved away and have not been heard from. In 5 cases, including three of first-infection tuberculosis, and two with minimal adult involvement, follow-up studies have been insufficient for either the patients' welfare or any conclusion regarding the progress of the lesions. Of the 7 remaining cases, results have been satisfactory in only three. One patient with an active, moderately advanced lesion refuses sanatorium treatment until lack of satisfactory results from home treatment render it necessary. In two patients with a childhood type of infection, the lesion has spread; yet continued effort to procure institutional care is unavailing. Although the disease is responding to treatment in the one remaining case, the time involved is much greater than would have been required had sanatorium care been instituted as soon as the diagnosis was confirmed. It should also be remarked that in at least two of the cases which terminated

fatally, even with sanatorium care, the unfavorable outcome is attributable to too protracted home treatment. In all three of the fatal cases, death resulted in spite of and not as the result of hospitalization.

From this analysis, even though it involves only 30 cases, it is evident that the care of the tuberculosis patient in the rural home holds forth little promise of desirable results. At once the question arises: What treatment has been instituted in the home? It has varied, depending upon the type, advancement and activity of the lesion. Some patients are not even permitted to feed themselves, while in some childhood lesions light exercise is allowed. Fresh air, sunshine and a high caloric diet are advocated and little medication is prescribed except for the more distressing symptoms. X-ray plates are taken every one to three months as necessary, and progress of the case is followed by someone specially qualified to interpret the films.

It is felt that it is not due to the treatment advised but to the treatment actually followed by the patient that the results are not encouraging. Minor variations in one phase or another could possibly be well borne, but each deviation soon leads to other concessions until the ultimate home treatment amounts to no treatment at all.

So it has long been the practice to urge sanatorium care in every case. Two factors prevent universal hospitalization. One is that patients wish to attempt treatment in the home before submitting to institutional care, and the other is that the cost of such treatment cannot be paid by the patient's family and will not be sanctioned by the proper county authorities.

If the patient desires to remain at home it is usually permitted only with the understanding that if, after a minimal period of heroic treatment, progress, as shown by repeated roentgenograms, is unsatisfactory, the patient will consent to care in a sanatorium. During such a trial-period the danger of infection of other members of the family and the difficulty of control of this danger become apparent to the patient. Realization of this fact, explanation to the patient of the educational advantages of sanatorium treatment, and the acquisition of knowledge pertaining to pneumothorax and operative procedures are often enough to convince both the patient and his family that treatment in a sanatorium is imperative.

Solution of the financial problems depends, of course, upon either provision of sanatoria in each county or the gradual education of the public to the necessity for this form of treatment so that permission can be obtained for such care in all cases.

In conclusion it may be said: first, that diagnostic problems of the general practitioner in dealing with tuberculosis are best solved by the adoption of a routine to be used in all doubtful cases. This schedule should consist of a careful history and physical examination, daily temperature record with readings taken at intervals of four hours over a period of ten to fourteen days, repeated sputum examinations, basal metabolic studies if necessary, tuberculin tests and roentgenographs. Second, that tuberculin tests and X-ray plates provide adequately for the investigation of the epidemiological features of cases found by the family physician. These procedures will be much more generally used if more intensively and extensively advocated and if some provision can be made for accurate interpretation of the films without additional expense to the patient or the rural physician. Third, that best results will be obtained both in control of spread of the disease and in reduction of morbidity and mortality, if tuberculous patients in rural districts are provided care in tuberculosis sanatoria.

THE BRONCHIECTATIC SEPTIC TANK

Its Prophylaxis and Treatment[1]

CHEVALIER JACKSON AND CHEVALIER L. JACKSON

Bronchiectasis, as the term is now used, refers not alone to a mere dilatation of a bronchus but to a chronic bronchial disease in which the dilatation is associated with [illegible]

CORRECTION

We regret the occurrence of an error in the paper by Barnwell and Pollard: *A Comparison of Old Tuberculin with Tuberculin Protein T.P.T.*, which appeared in our issue for October, 1934, vol. xxx, pp. 482–504.

The error is in table 3, lines C and D, page 489 of the issue. In line C "13.3" should read "42.6," and in line D "4.26" should read "13.3."

To these we suggest the addition of a fundamental factor that seems to have been largely if not entirely overlooked: namely (8), *the viscosity of certain pathological bronchial secretions.*

Of the various factors in these groups only the following will be considered herein, and of these only certain overlooked or rarely considered phases of their investigation: (1) methods of obtaining material for bacteriological study; (2) obstructions discoverable and removable by the bronchoscope; and (3) viscosity of pathological secretions.

[1] Presented at a joint meeting of the Chicago Medical Society with the Chicago Laryngological and Otological, and the Chicago Tuberculosis Societies and Aux Plaines Branch, November 1, 1933.

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Bronchiectasis, as the term is now used, refers not alone to a mere dilatation of a bronchus but to a chronic bronchial disease in which the dilatation is associated with certain clinical features, especially cough and purulent, usually foul, expectoration.

AETIOLOGY OF BRONCHIECTASIS

The causes of bronchiectasis have long been a subject for discussion, pathological studies, and clinical research. Certain causes are well known, even if not conclusively proved, and they therefore do not need comprehensive presentation here. There are a few features, however, that do not seem to be generally recognized; and it is to these we wish to call attention.

Broadly grouping the conceded aetiological factors we have:

1: Congenital factors,
2: Infection, including predisposing causes thereto, foci in sinuses, teeth, tonsils, etc.,
3: Pathological changes in the bronchial wall,
4: Pathological changes in the peribronchial tissues,
5: Obstruction: trachea, bronchi, glottis,
6: Stagnation of secretions,
7: Positive endobronchial air-pressure.

To these we suggest the addition of a fundamental factor that seems to have been largely if not entirely overlooked: namely (8), *the viscosity of certain pathological bronchial secretions.*

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BACTERIOLOGY

There are, roughly speaking, three groups of organisms in a well-developed bronchiectasis: namely (1) the primary organisms in the primary focus; (2) the secondary saprophytic organisms that reduce viscosity; and (3) the organisms producing the pus that results from irritation of the bronchial mucosa by the biochemical products of the saprophytes.

The last of these groups has not been generally recognized. When a mucous membrane, such as the bronchial mucosa, is kept in contact with any irritant material pus is produced; ulceration is not necessary; irritation, mechanical or chemical, will suffice. In the case of the bronchiectatic septic tank the biochemical products of the saprophytic organisms that are active in the reduction of viscosity irritate the mucosa and produce pus swarming with organisms. Obviously these are not the primary organisms.

Inoculation of the stagnant pus in the tracheobronchial tree with the putrefactive organisms is by way of the inspired air and also by means of the secretions of the mouth that are normally inspirated by everyone during sleep.

It is generally conceded that bacteriological studies of bronchiectasis have been extremely unsatisfactory and inconclusive. This has generally been attributed to oral contamination. There is another factor, however, that is even more important, namely, the *primary pus is not expectorated at all.* Its viscosity is so high that it cannot be coughed up. It remains in the bronchiectatic septic tank until its viscosity is reduced by putrefaction.

From the foregoing it is obvious that the method of obtaining the material for bacteriological study is of the utmost importance.

Methods of Obtaining Material for Bacteriological Study: Very interesting and important bacteriological studies have been made from tissues removed at lobectomy. These studies should be made at such operations; but we should like to emphasize the fact that an unlimited number of specimens for bacteriological study can be obtained without lobectomy or other operation, without contamination and without serious inconvenience to the living patient, by means of the bronchoscope. This statement, however, must be qualified by calling attention to the fact that to be of value a certain technique in the bronchoscopic procedure is essential (1). The bronchoscope is not only affording the bacteriologist

and the research-worker uncontaminated material for study and experiment; it is also the means of placing infective agents and other material in the bronchi of animals under various local conditions created artificially to simulate clinical and hypothetical conditions that may be contributory aetiological factors. The method of obtaining material previously described (1) (2) (3) seems of fundamental importance in these researches. This method consists in bronchoscopically aspirating the superjacent pus, which always contains a variety of secondary invaders. Then, when additional pus is forced in from the peripheral bronchi by the tussive squeeze, this is collected separately (4). In it the saprophytes are relatively few and the odor usually is absent. In the residual pus are usually found the important organisms, time after time the same in the same patient. This is in contrast to the confusing variety of organisms found in the superjacent pus and in sputum. That these are the important organisms is also evidenced clinically by the fact that vaccines prepared from them are of relatively much higher therapeutic value as compared to those from either sputum or the superjacent pus.

A search for primary aetiological bacteria in bronchiectatic sputum is parallel to a search for typhoid bacilli in material obtained from an efficient household septic tank instead of in material from a bed-pan.

VISCOSITY OF BRONCHIECTATIC SECRETIONS

It is interesting to note that a number of authors have called attention to the fact that bronchiectatic sputum is not adhesive; some call it "slightly tenacious;" others refer to it as "thin and comes up with little effort." These statements are to a certain extent true of *sputum*, especially as examined floating in saliva in a sputum cup; but *they are misleading as to the character of the pus when first produced in the bronchi.* The statements could be applied, also, in some cases, to the pus first encountered on introduction of the bronchoscope through the glottis; but this pus, in a typical case, has undergone physical changes that have greatly reduced the viscosity. As previously pointed out (4), after this thinner pus is aspirated the deeper pus is thicker and more tenacious; and when this in turn is aspirated the pus forced in from the periphery is of very high viscosity. It is so thick and clings so tenaciously to the glass walls of the collector that it will not run downward when the collector is inverted. Therefore it cannot be too emphatically stated that *the pus of bronchiectasis when first produced is of extremely high viscosity.* It is equally important to emphasize the fact that *this high viscosity is a basic*

aetiological factor in bronchiectasis. Because of it the pus cannot be efficiently expelled by cilia or bechic blast until its viscosity is diminished by putrefactive processes.

THE BRONCHIECTATIC SEPTIC TANK

By the term "bronchiectatic septic tank" is meant not only a receptacle for septic materials but a container where bacterial processes change the character of the contents in a way comparable to the processes in what the sanitary engineers call a septic tank.

That such secondary changes take place in the contents of bronchiectatic bronchi is a justifiable inference, not only from examination of the material as to viscosity but also from bacteriological studies of bronchiectatic secretions removed by bronchoscopic aspiration. Our bronchoscopic observations lead us to believe that these changes in the secretion constitute nature's way of rendering it easier of expulsion by reducing its viscosity. Unfortunately, however, they also render it more irritating and the stagnation of this irritating material promotes pathological changes in the bronchial walls, and thus constitutes an important aetiological factor in bronchiectasis. The bronchiectatic septic tank constitutes a fearful price to pay for drainage.

PROPHYLAXIS

From observation in hundreds of cases we feel justified in concluding that the disease we know as bronchiectasis is preventable by bronchoscopic aspiration instituted early in any suppurative disease of the bronchi. The removal of the viscid pus with a powerful aspirator will forestall the septic-tank processes that would otherwise ensue from inability of the cilia, cough and tussive squeeze to expel this tough viscid material. If, after the acute stage of any bronchial or pulmonary infection is over, there is not a progressive improvement in the signs, symptoms and roentgen-ray findings under medical care and management, including as it should postural drainage, bronchoscopic drainage once or twice a week will restore the defensive power of the lung. This turning of the tide, so to speak, has been observed in hundreds of cases at our clinic and it is frequent in the experience of every bronchoscopist; therefore mere coincidence cannot explain it. The bronchiectatic septic tank can be prevented in almost all cases if the start with efficient bronchoscopic aspiration be made early enough. Putrid bronchitis in our clinical experience is a preliminary stage rather than a distinct

disease; septic-tank processes are at work and unless prophylactic bronchoscopic methods are instituted the tanks will develop.

Two things should be added to the bronchoscopic aspiration: (1) the administration of vaccines prepared from the material bronchoscopically removed from the depths of the suppurative focus; and (2) the omission of drugs like opiates that annihilate the cough reflex and those like atropin that thicken the secretions.

Of utmost prophylactic importance is of course the elimination of infective foci in the teeth, tonsils and nasal accessory sinuses. It has been abundantly proved that in suppurative diseases of the bronchi and lungs the source of the infection is a focus in the region of the upper air-passages and there is much evidence to show that the route travelled is by the lymph-channels as well as the air-passages. Prophylactic measures, therefore, are wisely undertaken (1) before the onset of suppurative bronchial disease; (2) after the first bronchial symptoms; and (3) after bronchiectatic conditions have developed, to prevent reinfection and recurrence.

As in the prophylaxis of tuberculosis, all details of continuous medical care and management are of utmost importance; but they need no enumeration here. They should include prolonged daily rest in bed under outdoor conditions to increase resistance and build up a reserve.

It is of fundamental prophylactic importance for early diagnosis of every bronchopulmonary disease that every case of cough be run down to a definite cause and a definite lesion if possible. This is hypothetically admitted but practically it is not often done.

PROGNOSIS

The prognosis of bronchiectasis has been greatly improved by the use of bronchoscopic methods, especially (1) the study of the local pathological conditions in the particular case; (2) the elimination of the aggravating processes of the septic tank; and (3) the discovery and cure of obstructive conditions. By these methods the bronchoscope has placed bronchiectasis in the class of diseases that can be studied, not only by inference and autopsy, but by specular examination and biopsy, the class that can have the advantage of the addition of local measures to medical care and management.

In a general way it may be said that the prognosis as to cure depends largely on the stage of the disease. Early in its development bronchiectasis is, in most cases, curable. Late in the disease, large septic tanks

having developed, only palliation may be expected. Bilateral established bronchiectasis is less amenable to treatment than monolateral disease of similar extent. If nasal accessory sinus disease is associated, as it usually is, its curability determines that of the bronchial condition.

In cases with large septic tanks life may be prolonged, the patient may be restored to economic usefulness, and his social ostracism abolished, by periodic peroral aspiration.

TREATMENT

If prophylaxis has been neglected and septic-tank conditions have been allowed to develop treatment must be undertaken. The first step will be one or more bronchoscopic studies to determine local conditions as to (1) obstruction, by exudate, stricture, web, band, foreign-body, neoplasm or inflammatory tumor, granulations, granuloma, trabeculae, pockets; (2) the shape, size and extent of the septic tanks; (3) the condition of the tank-walls as to color, erosion, ulceration, granulations, granulomata, nodules, irregularities of surface or lumen, presence or absence of ring markings, adherent membranous or fibrinous exudate, source of blood and visible vessels, granulations or bleeding points; (4) the bronchi affected; (5) the undilated bronchi and their conditions; (6) the character and source of the secretions brought up from peripheral locations by the tussive squeeze and whence they come—trachea, larger bronchi, septic tanks, fistulae.

Often a number of bronchoscopic studies are necessary to determine all of the local pathological conditions present; at bronchoscopy separate specimens are taken of the superjacent pus and the residual pus. On the findings of all these studies in conjunction with the bronchographic findings the local treatment is based. Vaccines are prepared from the organisms predominating in the residual pus removed from the primary focus or foci. These are given under supervision of the internist or family physician in charge of the medical care and management of the case.

Bronchoscopic aspiration is done once a week, sometimes oftener. At each bronchoscopy local conditions are studied and dealt with as may be indicated. Local medication is introduced, using diluted neoarsphenamin, acriflavin, or one of a series of solutions worked out at the Temple University Research Laboratories by John Kolmer. After local conditions, especially obstructive, have been eliminated, catheter aspirations and medications may be used, the intervals between bronchoscopies being correspondingly lengthened.

It may be repeated for emphasis that the local bronchoscopic measures are an addition to, not a substitute for other methods of treatment. It is particularly necessary that medical care and management be continuous. Every detail of the patient's environment must be studied and his activities controlled. He must not be allowed to use up his gains in increased activities; on the contrary he must be kept in bed under outdoor conditions, 14, 16, 18 or more hours out of the 24, in order to build up a reserve and increase resistance. Postural drainage should never be neglected, and, if possible, it should be used at every coughing paroxysm.

One thing seems to us important: namely, that care be taken to avoid the use of drugs, such as atropin, that will thicken the secretions, and drugs such as the opium derivatives that will check the cough reflex, the watch-dog of the lungs. On the contrary, when the patient feels that a paroxysm of cough is coming on he should welcome it, immediately assume the most favorable posture and otherwise assist the expectorative efficiency to the utmost.

CONCLUSIONS

1. Bronchoscopic studies indicate that the two chief, primary causes of bronchiectasis are (1) excessive viscosity of the primary pathological bronchial secretions, and (2) the septic-tank conditions they engender.

2. By the term "bronchiectatic septic tank" is meant not only a receptacle for septic material but a container where the material is changed in physical character and bacterial content by bacterial processes, chiefly saprophytic, in a way parallel to the changes that are utilized by the sanitary engineer to change the physical character and bacterial content of household sewage.

3. The difference is that the concrete walls of the sewage septic-tank are not acted upon by the changed character of the contents, whereas the living walls of the bronchi are damaged by the inflammatory changes set up by the irritating character of the by-products of the septic-tank processes.

4. Putrefaction will ultimately thin the viscid secretions, so that they can be expelled by cough, but during the delay the septic-tank processes have ruined the structural integrity of the walls.

5. The chief means of preventing bronchiectasis is by forestalling the septic-tank processes by bronchoscopic aspiration of the viscid pathological bronchial secretions before they have time to rot.

6. The primary pus in bronchiectasis is not coughed up; hence, when

sputum is used, bacterial studies are misleading and autogenous vaccines are inefficient. The important organisms are found only in the residual pus removed bronchoscopically from primary foci after the bronchiectatic septic tank has been emptied by bronchoscopic aspiration.

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THE RELATIONS OF ALLERGY AND IMMUNITY IN A CLINICAL CASE OF PULMONARY TUBERCULOSIS

HENRY SEWALL AND KENNETH D. A. ALLEN[1]

More than two years ago one of us, through certain laboratory results (1), was led to suspect that the time-interval elapsing between two succeeding inoculations with virulent tubercle bacilli might hold the key to much of the obscurity that involves the relations of allergy and immunity.

We have assumed that in the human tuberculous patient reinfection from within, so often determined by muscular exertion, is closely analogous in its pathological reactions to reinfection from without as caused in the animal by bacillary inoculation.

As is well known, in the guinea pig a first infection with virulent tubercle bacilli, while symptomatically negative for several days, none the less very soon induces throughout the body a state of hypersensitiveness to tuberculoprotein. This hypersensitiveness continues to increase for a period which, with the dosage and culture used by us, we set tentatively at about 50 days, though it is well demonstrable in 7 days (2). When the hypersensitive animal is reinfected there is set up within a few hours a more or less violent local inflammatory response known as *allergy*.

We look on allergy as the expression of a double cellular attribute, *affective* and *effective*. The first is represented by the specific tissue hypersensitiveness induced by contact with antigen-protein, according to conditions of dosage and duration of action; the second is, figuratively, an explosive chemical reaction to a sudden reaccession of antigen-protein. This reaction may be either destructive or conservative for the host. We deduce from the experiments quoted above that in the early stages of hypersensitiveness the vital energy liberated by renewed contact with antigen causes much the same local tissue changes as would any nonspecific irritant, evoking immediate and violent inflammatory reactions directed to its sequestration and removal. But we found experimentally that, when the second dose of antigen was witheld for a

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considerable period (70 to 95 days), the violence of the local reaction to reinfection was diminished, although the amount of antigen was increased tenfold; and, when we examined the viscera of the animal months later, there was a lack of floridity in the lesions, while present were fibrosis and other appearances indicative of cure.

Accordingly we pictured an immunology in which the infecting agent more or less continuously operated on the host-tissues with a refinement of their hypersensitiveness and this, in turn, mediated cellular metabolism to the effect that quasipoisonous antigen became the specific stimulus for reactive and restorative processes resulting in anergy toward itself.

According to a general law of nerve-muscular physiology, first announced by du Bois Reymond:—it is not the absolute intensity of a stimulus but its *change* of intensity in time that constitutes an effective stimulus. We find the same rule curiously operative in the specific tissue reactions of the tuberculous, a fact apparently first empirically utilized by the clinical pioneer in sanatorium treatment, George Bodington (3), in 1840, but experimentally analyzed and therapeutically applied by Marcus Paterson in the first decade of this century (4). In other words, it seems that cellular resistance-immunity grows by *steps* in response to definitely renewed assaults of disease-provoking antigen, a thesis which will receive more extended exposition later.

Following the cue of specific intoxication then, we find in organisms capable of cure a definite sequence of responses as follows: (1) allergy; (2) protective reaction; (3) restorative reaction; (4) stronger immunity; and this we hope to illustrate by a clinical demonstration.

Case Report

Miss E. J. F., age 19, admitted to Presbyterian Hospital, Denver, November 21, 1926. Born in Kansas and lived in rural Colorado nine years.

Family history: Parents living and well; father a practising physician. One brother died 4 years ago of miliary tuberculosis. Another brother developed pleural effusion, probably tuberculous, a few months ago. One sister is apparently well. One maternal aunt, ill with tuberculosis, lived in the same house with patient about a year, 4 years ago.

Personal history: General health good; normal weight 190 pounds. Had measles, chickenpox and pertussis in childhood; otherwise healthy. Tonsillectomy in 1916, for no urgent cause. Four years ago was ill with supposed paratyphoid fever; had some fever; was in bed 2 weeks; convalescence was prolonged, but recovery was apparently complete under rest and with salol.

Catamenia began at 15 and continued regular and normal. In June, 1926, her menstruation was attended with great lassitude. She was accepted by the Presbyterian Hospital as a probationer nurse September 2, 1926.

Present illness: Early in October, 1926 patient had a "cold" and malaise. She failed to report this; two weeks later suffered severely from toothache; the third left lower molar was found abscessed and was extracted; companion tooth on right side received treatment. Patient now felt ill and developed cough, but continued on duty until November 21, 1926, when she was admitted to hospital as patient; her chief complaint was of pain in the back, headache, cough, general malaise.

Physical examination: A well-developed, obese girl. Face flushed, slightly cyanosed. Eyes, ears, nose, mouth, throat normal. Teeth good; tonsils missing. Neck and chest flushed, thyroid slightly palpable. *Lungs* show rather diffuse bronchitis, with many diffuse moist râles on coughing (has coughed 3 or 4 weeks). A small area in left subscapular region shows increased harsh bronchial breathing with crepitant and moist râles. *Heart:* Suspicion of faint mitral murmur; no arrhythmia. The pelvis, back, bones, joints, spleen, kidneys, reflexes seem normal. *Laboratory findings:* Urine negative. Blood, November 12, 1926, hb. 85 per cent; w.b.c. 8,000; December 31, 1926, hb. 75 per cent; w.b.c. 5,000 (polymorphs 79 per cent, lymphocytes 16 per cent, large lymphocytes 4 per cent, large mononuclears 1 per cent). *Sputum examination:* Negative for tubercle bacilli, December 9, 1926, but, two days later, and repeatedly thereafter, it was positive for tubercle bacilli. The laboratory report especially noted the "attenuated" form of tubercle bacilli when first discovered, contrasted with their subsequent normal appearance. *Diagnosis:* Pulmonary tuberculosis.

Comment: Patient's hospitalization lasted from November 21, 1926, to April 27, 1927, a period of 157 days. For the first month she received only general hospital care, making such exertions as were agreeable. It was late in December before a medical consultant (H.S.) prescribed immobilization.

Our patient may have started her pathological conflict unusually well equipped against tuberculosis, for her average weight of 190 pounds put her in the constitutionally hyper-resistant class, specified by Krause in an important paper (5). Nevertheless her immediate family history indicates rather extraordinary susceptibility to the disease. We think that the girl's good fortune consisted primarily in the violence, or, perhaps preferably, the lability of her specific allergy from the outset of her illness, which continued to assert itself after periods of slight exertion until fairly complete bed-rest was enforced, beginning nearly six weeks after her hospitalization.

We shall now describe, with brief running comments, the illustrative X-ray pictures of this case. Except for one bedside skiagram (figure 4, January 23, 1927) the patient was transported for pictures on a wheeling stretcher by elevator to an upper floor. Films were usually made with the patient sitting upright, but sometimes reclining at an angle. The first picture, figure 1, was taken December 7, 1926, after the patient had been nominally at bed-rest for 16 days. Her initial misery and fever, over 102°, had subsided after a week in bed. Feeling very well, she was allowed to sit up in a chair, a venture followed by temperature to 100° for 3 days; then normal until the first picture, which was followed by a rise in temperature lasting a week.

The first X-ray plate, figure 1, showed nothing distinctly pathological except a thick-walled elliptical area left of the heart and in contact with its border. Subsequent study of this formation led to a definite opinion that it was a large cavity located in the posterior part of the lower lobe of the left lung in mid-dorsal region.

Figure 3 shows a lateral view of the lesion, between the ink-marks on the spine, taken December 21, 1926. This cavity, if such it was, must have drained freely since very little fluid was ever determined in it. It evidently had presented physical signs to auscultation, detected by the House Physician, Dr. Hazen, at her first examination. We may be justified in suspecting that the cavity had its origin in a nodule of primary infection, developed during the known exposure of the patient some years before or antecedent to this. It seems plausible that it may have been activated by toxaemia resulting from the abscessed tooth extracted October 26, 1926, and it may have caused the backache, a prominent initial symptom. We cannot positively exclude the suspicion that the lesion we call a cavity may have been interlobar in origin; such presumably may have been caused by ulceration of a primary nodule contiguous to the interlobar pleura. Covered by the 9th rib on the right side appears to be another Ghon node.

We will assume that the primary focus of our patient's disease was seated in the demonstrable so-called cavity in the lower lobe of the left lung. We may suspect that a Ghon nodule here had for a good while been insidiously changing into an active focus. The history remarks an illness, thought to be paratyphoid fever, which prostrated the patient four years before her hospitalization under our care; this may well have marked a stage of tuberculosis. Again, six months before this record begins, the patient was impressed with the undue lassitude experienced with a menstrual period, possibly a symptom of tuberculosis.

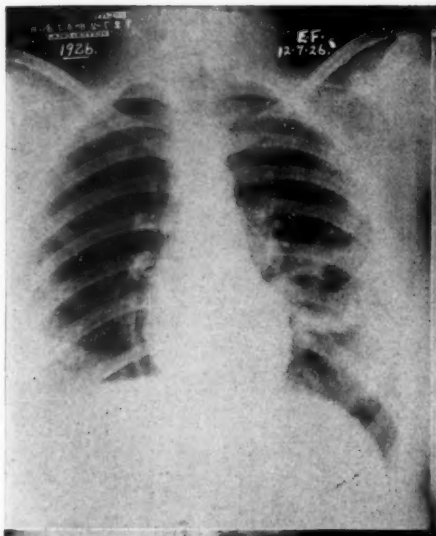

FIG. 1

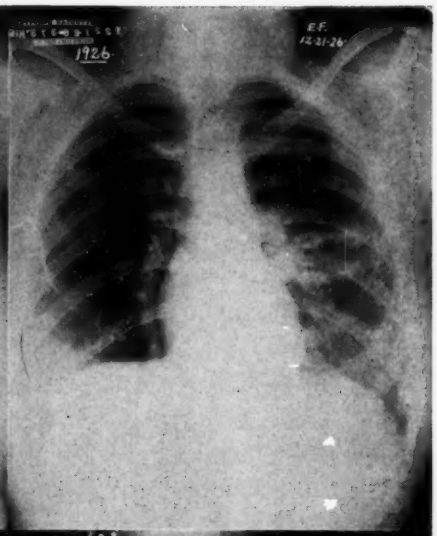

FIG. 2

FIG. 3

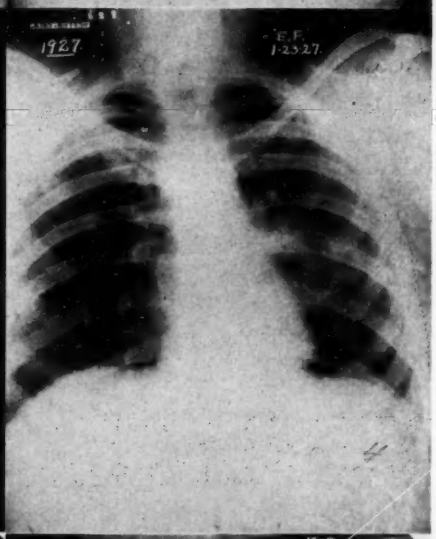

FIG. 4

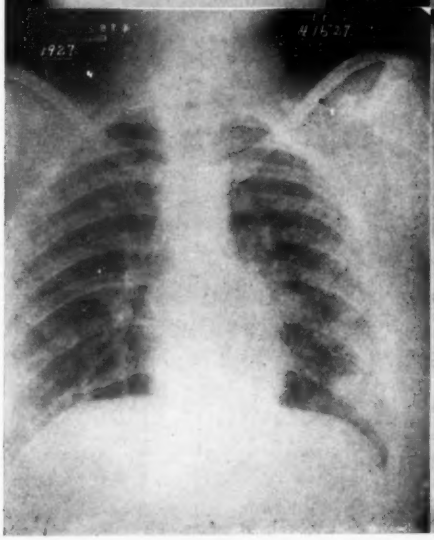

FIG. 5

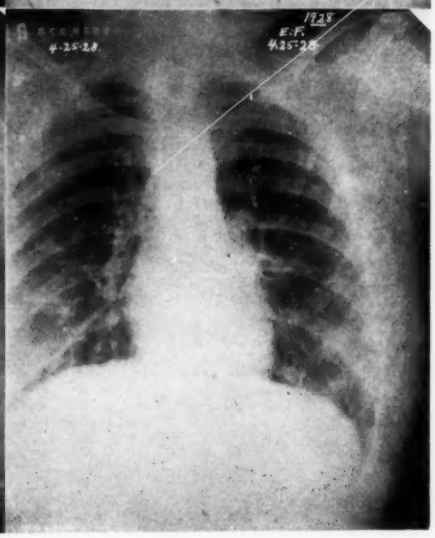

FIG. 6

It may be recalled that an experienced laboratory pathologist in his first report of tubercle bacilli in the patient's sputum had definitely remarked on their "attenuated" form. No conclusion will be drawn from this observation, albeit many years before one of us (6) had sought to point out a relation between the tubercle-bacillary morphology in sputa and tuberculous clinical activity.

So far as it goes, the laboratory report of our patient's sputum tends to confirm her past history and our interpretation of her earliest X-ray plate, namely, that for a considerable period, probably four years or more, she had lived under the immunizing influence of a *primary* tuberculous infection of low virulence.

Figure 1 shows on the left side the extensive area we have designated a cavity, with a capsule suggestive of an areola of intensely congested tissue or deposit. At the same time there is marked opacity, probably connoting allergic inflammation, through the base of the left lung. The left hilum also shows some hyperaemia. The right lung may tentatively be regarded as normal at this stage, although a latent Ghon nodule is seen in its base.

Figure 2 represents the condition just two weeks later, December 21, 1926. When the first picture was taken the patient's temperature had been normal for five days, but doubtless the exertion attending the X-ray examination initiated a period of allergic excitement with fever, much intensified during a menstrual period, which accounts for the changes noted in figure 2. These changes consist in a notable increase and extension of the diffuse cloudiness of the left hilum, with marked congestion of the lower half of the left lung, while at the same time the cavity appears to have become distinctly smaller. The picture shows intense allergic excitement by contiguity; there are few if any new-formed tuberculous deposits, but the inflammatory state of the left hilum and of the cavity seems to spread over the base of the lung, suggesting the appearance following an overdose of tuberculin.

At the same sitting lateral views of the chest were obtained (figure 3) showing the outline of the wall of the cavity against the bodies of two mid-dorsal vertebrae, between ink-marks; across the posterior mediastinum the involvement of the lung bases is also seen. Corresponding with the signs of increased allergic reaction in the left lung, the toxic symptoms of the patient became accentuated.

The next X-ray picture was taken nine days later, December 30, 1926, just at the end of a week's fever. The picture is not reproduced here,

since it is not materially different from the preceding; but the exertion attending its production caused clinical evidences of an intense allergic reaction, lasting ten days, with symptoms of nervous and gastrointestinal intoxication.

By this time it was fully realized that even the slightest exertion was apt to be followed by illness and a spell of fever, with the sequel of a normal to subnormal temperature as soon as the flurry was over.

The next picture, figure 4 (January 23, 1927), was taken at the bedside and followed 33 days after figures 2 and 3. This period, as has been noted, was marked by considerable allergic disturbance, mostly attributable to slight muscular exertion, but followed by an afebrile state lasting two weeks which was terminated by a sharp fever attending the onset of menstruation.

Considering the condition shown in figure 2 (December 21, 1926) and the subsequent clinical turmoil of the patient, we would naturally expect to find in the last picture, figure 4 (January 23, 1927), the evidences of new parenchymatous tuberculous deposits, marking extension of disease in the left lung. On the contrary, there is in figure 4 not only no evidence of new deposits in the lower left lung, but configurations formerly apparent seem to have disappeared; there is also a sharpness of outlines in the left hilum, which connotes a diminution of allergic disturbance. On the whole there is rather notably less tuberculous activity in the *left* lung than was obvious a month before.

But on the *right* side at the apex, under the inner half of the clavicle, there is now a portentous shadow, an inflammatory congestion which undoubtedly signifies that infection had advanced to the right lung. This is a striking confirmation of Krause's dictum (5): "Within the same body foci in one organ will be healing as those in another part are exhibiting signs of floridity."

Returning to an immunological consideration of the left lung:—there is visual evidence that the lower lobe has, from the very beginning of the infection, been in immediate proximity to the source of allergizing and immunizing bacillary products. That this viscus has not become completely tuberculized indicates that its acquired immunity was very high, for it is hardly credible that the base of the left lung should not have been more or less showered with tubercle bacilli.

There is considerable evidence (Amberson (7), Jaquerod (8)) that tuberculous deposits, even when fairly dense, may undergo resolution through some sort of immunological chemistry. How credible then is

the suspicion that lytic antibodies, or what not, have in this area, the lower lobe of the left lung, nearly or quite *prevented* the formation of tubercle altogether. Here then we have, *for the time being*, an example of perfect *resistance*, *protective immunity*. At the time the fourth picture was taken, January 23, 1927, the patient was "turning the corner" from her illness, though we did not know it. The sputum, thick and abundant, diminished and occasionally ceased for a day. A feeling of well-being developed late in January, and menstruation, which had not ceased to appear, in February no longer caused fever or malaise.

Continuous bed-rest was still maintained. After the first week in February the temperature ceased to rise above normal.

The first adventure to test the soundness of this progress was transportation of the patient to the X-ray room on April 16, where the film for figure 5 was produced April 16, 1927. The note of the roentgenologist (K.D.A.A.) briefly describes this picture: "Cavity healed. Entire right upper lobe involved." Comparing this picture with figure 4, from a film made 83 days before, we find that the whole left lung within this period has been fairly well cleared of pathological deposits, the ring of the obliterated cavity being represented by a small cloud under the left hilum.

But in figure 5 the right lung, which in the previous picture showed only vascular congestion at the apex, now shows the whole upper lobe mottled with tuberculous deposits, which spread well into the lower lung. We had postulated for the right lung a hypersensitivity which would respond to contact with tuberculoprotein and cause its fixation, but with too feeble immunity to immediately destroy it, in contrast with what had occured in the left side. In short, the upper lobe, and more, of the right lung is thoroughly tuberculized.

The fate of these tubercles, and of their host, was to be determined by two sets of conditions: (1) the specific antibacterial power of the blood and of the tissues; (2) the shifting immunological environment of the seat of the conflict, which to a large extent is determined by the behavior of the patient himself. It includes all the known hygienic factors, food, ventilation, etc., but above all it predicates management of *Rest* and *Exercise*, by which may be regulated to a nicety the time and intensity of allergic stimulation of the hypersensitive foci. Krause asserts: "Generalized miliary tuberculosis strikes down most commonly (if we except infants) persons who have previously had no manifest tuberculosis" (5). This would indicate that tuberculohypersensitiveness

favoring precipitation of tubercles may arise from very mild infection and far outruns the effective curative reaction of immunity.

If our view of the immunological determination of the localization and fate of tuberculous deposits in the contralateral lung is correct, we cannot fail to extend it to the explanation of the apical localization of the so-called *adult type* of tuberculosis, with, perhaps, consequent uncovering of new points of observation.

We return now to the clinical aspects of our case. The patient was not disturbed by the exertion attending the X-ray on April 16, 1927, and her condition seemed steadily to improve; nevertheless the picture of that date, figure 5, showed extensive fresh tuberculous deposits in the right lung, which bespoke caution as regard to exercise. Her release from the hospital has already been noted as of April 27, 1927, when by ambulance and railway she was conducted to her home, some hours distant. There, with admirable understanding of her problems, she remained completely bed-fast for three months before, at the end of July, beginning gradually to get up for meals, ablutions, etc. This cautious life was continued to September, 1928, when she entered a teacher's college, but still leading a quiet life.

As already described, the patient had returned for X-ray examination, April 25, 1928, one year after leaving the hospital (figure 6). The remarkable clearing up of the whole lung, especially as regards the upper lobe on the right, is ample evidence of the house-cleaning and restorative power of constructive immunity. We might defensibly assume that the view presented in figure 6 indicated that the patient's campaign against tuberculosis was a closed book, were it not that more than four years later, June 15, 1932, another X-ray film continues the story (figure 7). This picture may be analyzed before referring to the patient's contemporary life.

Figure 7, as to the left lung, seems to confirm our view of the powerful immunity developed near the site of the primary infection, as of an aggressive protective power which did not wait on the bacillary invaders to entrench themselves in tubercles, but attacked and destroyed them at once when sensed. Nothing remains of the imposing cavity, except perhaps a few inert nodules. On the right, where we had seemed to recognize a lower intensity of immunity, or rather a more leisurely and probably more complicated immunological operation, we are intrigued, as always, to find evidences of infection far more abundant than anticipated. For, in figure 6 it had appeared that infectious foci had been pretty effectually cleared out, but the plate taken four years later

shows great numbers of tiny calcified or densely fibroid spots of healing. There was nothing in the clinical history of the patient during the four years intervening between the last two pictures which would indicate an interruption in the course of her cure, although in the interval she had undergone general anaesthesia and appendicectomy (1929) with complete recovery.

It remains to touch upon the general manner of life of our patient during the seven years since her active clinical tuberculosis began, or

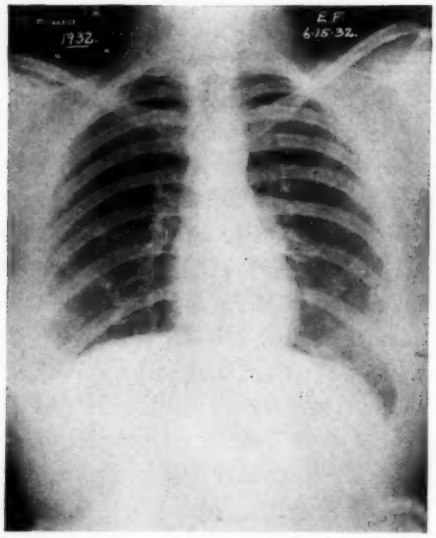

FIG. 7

was recognized. In letters dated October to December, 1933, she writes that her present weight is 175, though normally 190 pounds.

She has no morbid symptoms or any undue fatigue. She began teaching school the fall of 1931 and "averages at the very least 9 hours a day." "I feel better than I have for years—I lead a much more active life which perhaps accounts for it. . . . I am not subject to colds and have never missed a day of school." Her exercise is walking and horseback riding, and her school-work "is not a 9 to 4 job."

DISCUSSION AND SUMMARY

We have traced by clinical record and by anatomical picture a case of adult type of pulmonary tuberculosis from a florid beginning to an apparently happy end.

We would qualify the familiar pioneer views of A. K. Krause on the relation of allergy to immunity by stressing the fundamental importance of the time-intervals between successive inoculations of antigen, and also the magnitude of dosage.

We find helpful a conception of the development of immunity in an organism as a course of education in which tissue cells are pupils which require ample time and intensive training to be prepared to meet and overcome the agents of tuberculosis.

The art of the clinician consists in regulating the metabolic tasks of his patients so that no living cell is ever endangered by too large or too frequently administered doses of antigen. His value to the patient still is measured by the wisdom of his empiricism.

The sketch we have presented justifies no dogmatism as between the therapeutic virtues of Rest and Exercise; they are but different temporal components of the same restorative regimen, to be applied critically for their effects, and with reference to local and general conditions in the patient.

It seems to us that conceptions like those of Marcus Paterson (4) should be considered, whether practised or not, in most clinical cases.

We have been led to wonder whether the prolonged general immobilization necessary to subdue tuberculous activity in a restricted area does not seriously impair the natural defensive powers of the healthy tissues. Possibly a major virtue of effective artificial pneumothorax consists in the latitude allowed for preserving normal physiological responses.

That view of the pathological conflict seems to us most practical which conceives it as an immunological sequence, in which antigen, the active inciter of disease, is the very agent responsible for the antitoxic organization and operation of the patient's tissue cells. Our radiograms have depicted a history which develops a definite meaning when interpreted on this basis.

In our patient we seem to have witnessed the very crossing of the threshold separating the primary from the secondary or adult type of pulmonary tuberculosis; for we confidently assume that our patient's illness was symptomatic of her first major microbic assault involving the massive liberation of tubercle bacilli among tuberculohypersensitive tissues. Thereafter, our reasoning was checked with objective observations.

The clouding of our films in the vicinity of obvious foci of infection could only be interpreted as due to inflammatory (allergic) congestion.

We found a direct proportion between physical exercise, focal congestion and pathological symptomatology in our patient's early records. The first evidence of extension of infection from the left to the right lung was witnessed by a cloud betokening allergic reaction, following which were the morphological condensations in tubercles, the which, entirely under a therapeutic regimen of rest, became dissolved or mineralized *in situ*.

Notably the allergy, so labile and outstreaming from the foci of infection early in the disease, spontaneously disappeared after an adequate period of rest and failed to return later under vastly increased exertion. That is, given time and abstinence from functional calls, the infected tissues reacted with adaptations that restored physiology. "Education" was successfully completed.

But in deference to logic it must be admitted that the teleological rôle we have imputed to allergy is based on circumstantial evidence. This disturbance *may* possibly be only an accidental concomitant of disease or its healing, a view ably supported by Rich and McCordick (9).

Finally, it should be emphasized that in the case-history presented above the factors of the pathological problem were reduced to relatively simple terms; therein consists its pedagogic value. In actual experience the clinician is confronted with the variables comprising tuberculosis in many confusing permutations and combinations:—so much the greater, therefore, is his need for standard units of measurement.

We desire to acknowledge indispensable aid in the preparation of illustrations given us by Dr. H. J. Corper.

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THE FUTURITY HANDICAP OF THE TUBERCULOSIS CONTACT[1]

A Consideration of Data Relative to the Pre-Assessment and Prevention of Clinical Disease

A. H. W. CAULFEILD AND G. C. ANGLIN

The means by which we will attempt to forecast the probable development of clinical tuberculosis in tuberculin-positive individuals (contacts) is through the use of serial serological tests.

Before presenting graphs so obtained we feel it is necessary to very briefly present data obtained by the use of these two serial tests carried out over a period of time upon clinical cases of tuberculosis. These results (upon actual cases) will be used as a sort of yard-stick by which to measure, or differentiate between, tuberculin-positive individuals (most of whom were instances of known contact).

The results upon clinical cases are presented as part 1, and the application of these findings upon contacts (tuberculin-positive individuals) as part 2.

Part 1

RESULTS OBTAINED WITH SERIAL SEROLOGICAL TESTS IN CASES OF CLINICAL TUBERCULOSIS

The two tests used are the inhibitive and the tuberculocomplement fixation. The latter has been tried and discarded by most clinicians and the former, given scant trial, has nevertheless been considered unsatisfactory.

The T. C. F. as an immunological method is so well known that no explanatory comment seems necessary. The inhibitive test is relatively unknown. It was first reported upon by one of us (A. H. W. C.) in 1911.[2] For our present purpose it seems sufficient to state that it is a test-tube reaction with the patient's serum: and similar to complement-

[1] Presented at a Clinical Session of the thirtieth annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, May 16, 1934, and to Section of Medicine, New York Academy, October 17, 1933.

[2] Proceedings of the Royal Society, B., 1911, vol. lxxxiv.

fixation in that antigen, serum, complement, and sensitized corpuscles are used. It has been claimed that with sera from the tuberculous a positive result is usually obtained in a periodical fashion only, and that rarely does one obtain positives on consecutive repetitions.

Most who have attempted to use serological tests elsewhere have found them unsatisfactory chiefly because they did not give the results expected by the physician. In other words, the clinician demands that a satisfactory laboratory test should give about 100 per cent positive results in clinical cases and about 100 per cent negatives in all individuals in whom tuberculosis cannot be demonstrated. Any other result is regarded as indicating the lack of practical value. Serial tests have not been used that we know of except in Toronto. Thus we would seem to be the only group in a position to make a comprehensive fact finding analysis, irrespective of what might be regarded as desirable or of practical clinical value.

To obtain our serological yard stick (based upon the findings in cases of clinical tuberculosis) we decided that our purpose would be fulfilled by taking only those cases in each of which

(1) an observation period of 5 years or more had been completed;[3]
(2) ten tests or more had been done;
(3) either tubercle bacilli had been reported from our own laboratory or an irrefutably positive X-ray opacity had been found; and
(4) definite treatment had been instituted for a period of time.

Files were drawn alphabetically and accepted or rejected according to these four specifications. Definite as these would seem to be, an occasional case presented features which left one in doubt as to the propriety of its inclusion.[4] The results obtained in 50 consecutive cases are shown in table 1.

To fulfill these four requirements, many of the cases necessarily varied about the "Apparently Arrested" type for a considerable period of their observation. It seemed, therefore, desirable to obtain a more acute or clinically active group as a contrast.

To obtain this we drew the files alphabetically of all cases admitted to the tuberculosis ward of a general hospital (C. S. H.), accepting all, provided the sputum was positive during residence. Nearly all were

[3] On consulting the serological card-index it was found that over 800 clinical cases, not necessarily tuberculous, had had 10 tests or more and had been under observation for 5 years or more. From 1920 until January, 1933, 12,134 cases or individuals have been tested with a total of 34,928 tests.

[4] See graph 1.

febrile and had been admitted temporarily and usually because of an exacerbation, haemoptysis, or for some type of collapse.

Some had only a few serological tests; others had many. The results obtained are included in table 1, and differ so slightly from the group of routine cases that there seemed no reason to increase the compilation of this latter group. As shown in chart 1, the yard-stick obtained in clinical cases was approximately 50 per cent positive results with the T. C. F., and 20 per cent for the inhibitive test.

After consideration we concluded that the results obtained upon normals,[5] who had been found to be tuberculin-negative, should provide the best type of control to the results obtained upon the two clinical groups; and should give an accurate indication of the degree to which the tests gave "false positives." In other words, the percentage of laboratory error in individuals who must, with the minimum of reservation, be regarded as yet uninfected with the tubercle bacillus.

We found on consulting the laboratory cards that approximately 300 normals, composed of 239 medical students, and 51 nurses, doctors, and laboratory assistants, had been tested by tuberculin and had had one or more serological tests done. Of this number 53 had been found, on a total of 127 tuberculin tests,[6] to be negative to tuberculin. The results are incorporated in table 1.

Table 1 shows very definitely that clinical cases, on an average, do not give anything like 100 per cent positive results with either of the tests but nevertheless they do show a marked contrast to what is obtained with tuberculin-negative individuals. In compiling the results upon the clinical cases it was manifest that far-advanced cases *may* give exactly the same type of serological graph as those with minimal degrees[7] of involvement.

[5] The results on the first group of students were published in the *American Review of Tuberculosis*, August, 1925, xi, no. 6; a second and larger group of 143 are now under observation by Doctor Gordon and Doctor Norwich.

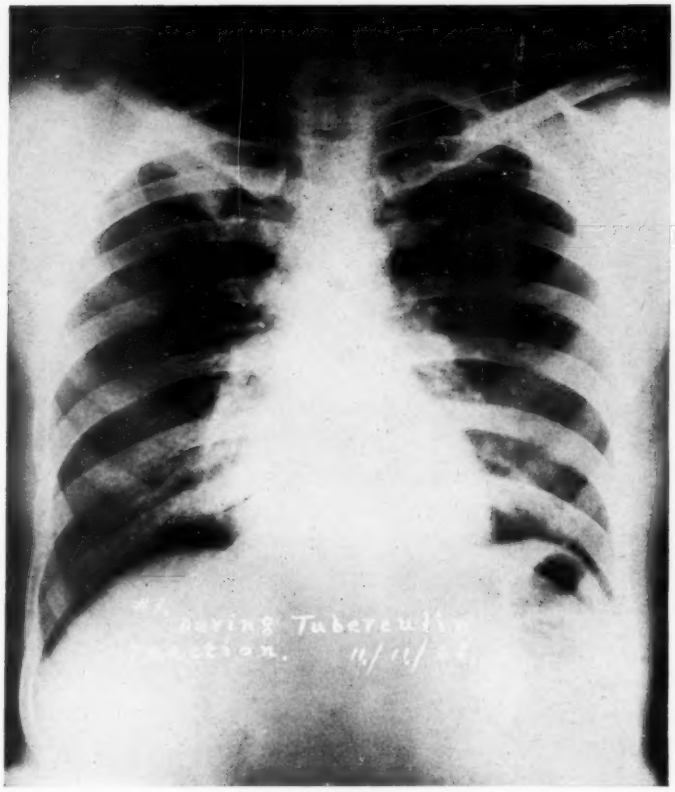
[6] The intracutaneous test of Mantoux has been used throughout. All batches of tuberculin have been made locally (Connaught Laboratories, University of Toronto) and standardized against the preceding lot by intracutaneous testing on human beings or infected guinea pigs or by both methods. The only difference is that for the last half-decade the bacillus has been grown on synthetic media. The routine has been to give 1/20 mgm. in the first dose and 1/4 or 1/2 mgm. in the second or third doses, if the first injection gave none or a doubtful reaction. The tuberculin has approximately the same degree of potency as compared with the International Standard Tuberculin.

[7] On immunological grounds there is no reason to expect that positive serological tests should be restricted to that ill-defined group which we label as clinical, and should not be found to an unknown percentage among the tuberculin-positive "normals."

If the same types of positive serological results may be obtained in the far-advanced cases as in those of minimal involvement, it seems logical to infer that similar types of serological results may be obtained in an unknown percentage of apparent normals (who are tuberculin-positive) with a nondemonstrable lesion, which has not been eradicated, irrespective as to its induction of symptoms. We must confine ourselves to showing that the former does take place by the cases selected for illustration, stating that such could be multiplied; and suggest that the inference is a logical introduction to the second part of this paper.

The serological graph records 7 end-results for each test. Those recorded from the 5th line up are regarded as positive and given the value of 1 in computing percentages. The 4th line result is regarded as weakly positive and given the value of $\frac{1}{2}$. End-results charted on the 1st, 2nd, and 3rd line are regarded as negative. Absolute normal for the T. C. F. test is the 1st line and for the inhibitive test the 2nd line. An almost perfectly normal series is shown in graph 5, part 2.

As an aid and as well as an introduction to a short discussion of the figures shown in table 1 five cases with summarized histories are presented as illustrative of the varied types of serological graphs found among the 50 routine cases of clinical tuberculosis.



Name C.E.T. No. 1

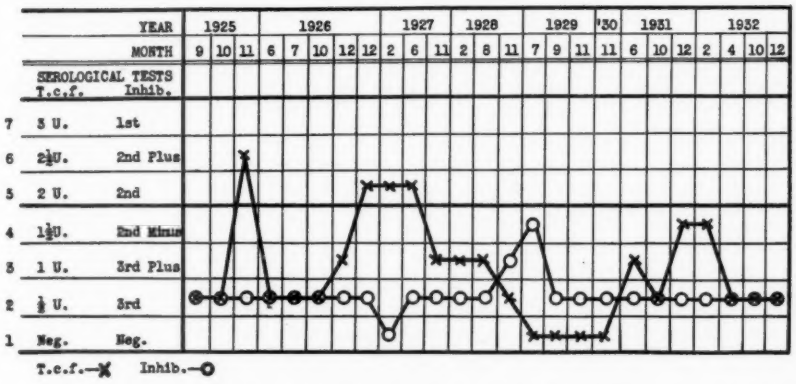
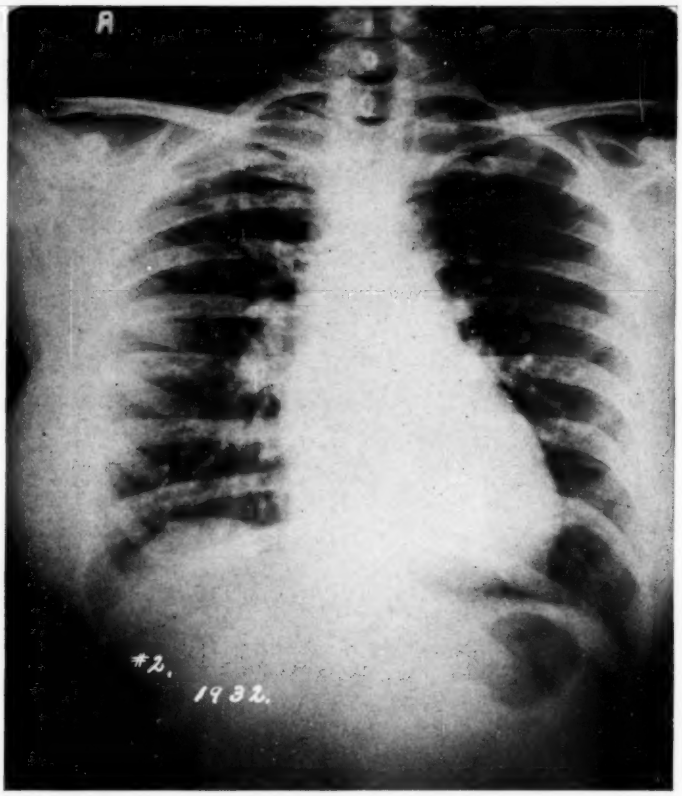


FIG. 1 AND GRAPH 1. C. E. T. (A serological graph and one X-ray reproduction.) The 1st X-ray (taken 22.10.25) showed a very questionable subapical opacity. The 2nd X-ray (11.11.25) shows a definite focal reaction obtained during a general reaction to tuberculin used diagnostically. This case, it was felt, should be included in the clinical group as it fulfilled the four requirements laid down. It is chosen for illustration as it demonstrates several features, namely, (a) during and for some time subsequent to the tuberculin reaction the graph is of the positive type; (b) the X-ray opacity has been completely absorbed for some years now and the patient is living a perfectly normal life, which corresponds with the almost normal graph obtained ever since 1929. The inclusion of such cases naturally reduces the percentage findings but in such instances the persistence of negative tests is extremely helpful in that it reinforces the clinical conclusion that the individual is "apparently cured." A continuance of normal serological findings together with clinical well being as far as tuberculosis is concerned would support the use of the classification "cured." We have such illustrations but they did not occur among the 50 cases analyzed.

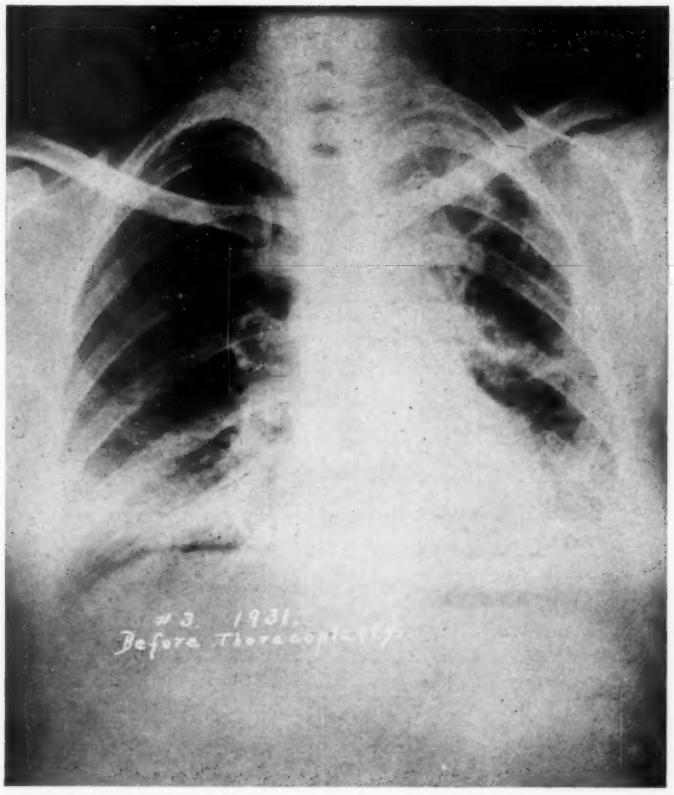


Name W.H.E. No. 2

		YEAR	1924		1925			1926				'28	'29	1930		'31	1932		'33
		MONTH	7	9	2	7	9	1	5	8	10	1	10	6	12	3	5	11	3
	SEROLOGICAL TESTS T.c.f.	Inhib.																	
7	3 U.	1st																	
6	2½U.	2nd Plus																	
5	2 U.	2nd																	
4	1½U.	2nd Minus																	
3	1 U.	3rd Plus																	
2	½ U.	3rd																	
1	Neg.	Neg.																	

T.c.f.—X. Inhib.—O.

FIG. 2 AND GRAPH 2. W. H. E. (A serological graph and an X-ray reproduction.) When seen originally, 1924, this case showed a small apical involvement without evident cavitation, had positive sputum and definite symptoms leading to medical consultation. During a short period of sanatorium treatment the symptoms disappeared and the sputum became negative. Since then she has increasingly assumed a normal type of life, and on the few occasions when sputum has been present it has been negative. Despite this the opacity has not cleared and cavitation is probably present. The graph is of the type that is frequently obtained with similar types of cases. The X-ray presented was obtained in 1932.



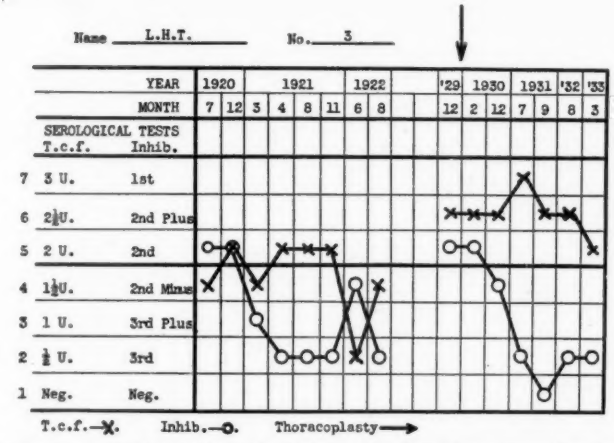
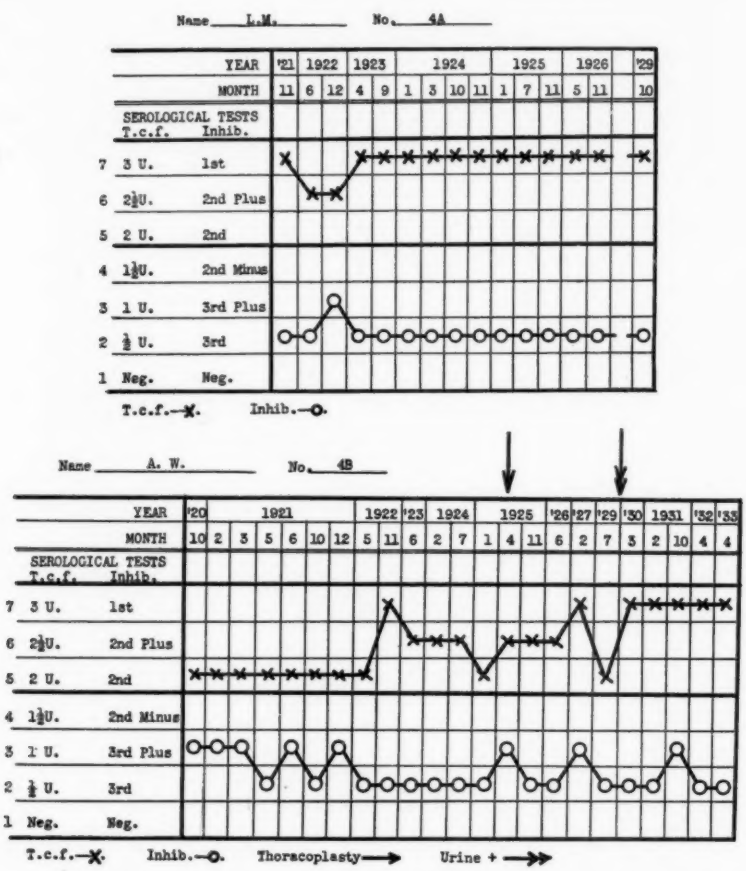

Name L.H.T. No. 3
YEAR 1920 1921 1922 '29 1930 1931 '32 '33
MONTH 7 12 3 4 8 11 6 8 12 2 12 7 9 8 3
SEROLOGICAL TESTS
T.c.f. Inhib.
7 3 U. 1st
6 2½U. 2nd Plus
5 2 U. 2nd
4 1½U. 2nd Minus
3 1 U. 3rd Plus
2 ½ U. 3rd
1 Neg. Neg.
T.c.f.—X. Inhib.—O. Thoracoplasty

FIG. 3 AND GRAPH 3. L. H. T. (A serological graph and an X-ray reproduction.) This case when seen originally in 1920 had a minimal left apical lesion. Relative well-being followed rest but progress subsequently was not satisfactory up till 1922. In 1929 her history since 1922 showed she had had a varied mixture of well-being and exacerbations—pneumothorax had been obtained and lost. She was then in 1929 febrile with positive sputum. A thoracoplasty done then by one of us (A. H. W. C.) has resulted favorably and since then there have been no exacerbations and the sputum has remained negative.

The serological graph during the early years when the lesion was minimal is of the same type as that obtained just before and after the thoracoplasty was done. Further it is similar in type to the preceding graph 2. On the basis of the graphs neither case should be classified further than apparently arrested despite the well-being, work capacity and negative sputum.


Name L.M. No. 4A
YEAR '21 1922 1923 1924 1925 1926 '29
MONTH 11 6 12 4 9 1 3 10 11 1 7 11 5 11 10
SEROLOGICAL TESTS
T.c.f. Inhib.
7 3 U. 1st
6 2½U. 2nd Plus
5 2 U. 2nd
4 1½U. 2nd Minus
3 1 U. 3rd Plus
2 ½ U. 3rd
1 Neg. Neg.
T.c.f.—X. Inhib.—O.
Name A. W. No. 4B
YEAR '20 1921 1922 '23 1924 1925 '26 '27 '29 '30 1931 '32 '33
MONTH 10 2 3 5 6 10 12 5 11 6 2 7 1 4 11 6 2 7 3 2 10 4 4
SEROLOGICAL TESTS
T.c.f. Inhib.
7 3 U. 1st
6 2½U. 2nd Plus
5 2 U. 2nd
4 1½U. 2nd Minus
3 1 U. 3rd Plus
2 ½ U. 3rd
1 Neg. Neg.
T.c.f.—X. Inhib.—O. Thoracoplasty Urine +

GRAPHS 4A AND 4B. (Two serological graphs.) Both cases were moderately advanced in pathological involvement with positive sputum. Both are now sputum-negative for some years, living in the instance of 4A an almost normal life and in the case of 4B a partially protected life. In 4A the opacities have undergone considerable absorption. In 4B the sputum became negative after a thoracoplasty performed in 1926 by one of us (A. H. W. C.). No evidence has been obtained of clinical tuberculosis of the kidney despite the fact that there was at one time suspicion of this with once the positive demonstration of *B. tuberculosis* in the urine (positive guinea-pig inoculation). Both graphs help raise the percentage findings for the T. C. F. test and lower the results for the inhibitive test: the graphs are, however, typical for these types of cases, chiefly in that neither has during the period depicted had a definite exacerbation of their tuberculosis. In the group of 50 cases analyzed there is at least one case of minimal involvement (which has largely but not completely been absorbed) whose graph is an exact duplicate of 4A, a definitely moderately advanced degree of involvement. X-ray reproductions are not given because they would seem to serve no useful purpose.

TABLE 1

Percentage of positive results with serial serological tests on two groups of clinical cases of tuberculosis and on tuberculin-negative normals

SEROLOGICAL TESTS	50 ROUTINE CASES UNDER OBSERVATION	30 BED CASES	53 TUBERCULIN-NEGATIVE NORMALS
Total number of tests	625	300	182
Positive T.C.F.	342 (54%)	144½ (48%)	25 (13%)
Positive inhibitive	115 (18%)	67 (22%)	2½ (2%)

DISCUSSION

Before attempting to show any application from the data obtained on clinical cases it would seem advisable at this point to further explain the results presented; namely, the percentage figures of table 1 and the significance of the graphs used for illustrations.

The percentage findings shown in table 1 give, of course, the average for each group. This means that the results obtained in individual cases fall above and below this average. The average number of positive tests with clinical cases is respectively only 50 per cent and 20 per cent (approximately) for the two tests, so that in certain cases it will be lower than one or other of the percentages obtained with the normal group.[8] Partly to show this, we selected 5 cases for illustration,—as typical as may be of the different types of variation obtained. Each type of serological graph we believe correlates with its own clinical type to a considerable degree. We believe this to be true even though on first thought it may seem to contradict the statement that identical types of graph may be obtained irrespective of the extent of pathological involvement as judged by X-ray films. While it is not the purpose of this paper to show correlation between types of serological graphs and clinical courses, this conception is to an extent necessary in explaining the manner in which we will attempt to show application in the second part of this paper. Expressed differently one must not only consider the percentage figures (table 1), but as well get the impression which we hope the selected illustrations convey. At this point it seems advisable to stress the fact that the percentage figures given in table 1 refer to the number of positive

[8] The percentage figures for tuberculin-negative individuals are probably unfairly high. This is due to the fact that if a positive result was obtained in the first test an unusual endeavor was made to repeat the tests. Such an individual frequently gave the same results in subsequent tests. Taking only the first test for each individual the results were approximately 8 and 5 per cent respectively.

results obtained in the series of tests, and not to the number of individuals who gave positive tests in the three different groups. With the 50 "routine" cases of tuberculosis all have had 10 tests or more; with the hospitalized group (probably more active) no restriction on the number of tests was possible; and the same applies to the tuberculin-negative group of normals.

The application is seemingly rendered more difficult because the results of two tests are considered simultaneously. Further, the illustrations show that with clinical disease there is a type of case in which one of the tests (usually the inhibitive) consistently remains normal, or at best gives only an occasional positive.

Thus one can only conclude that on analysis, clinical cases do not give an exact serological yard-stick. The variations found in individual cases not only prevent this but demonstrate also how misleading a single test may be. It can, however, be stated that practically all of the clinical group gave what we regarded as a positive type of graph, if the latitude is afforded of disregarding negative results when this conformed to the disappearance of clinical evidence such as is illustrated in graph 1.

The conception of the use of serological tests (such as the two under consideration) has been based by the profession on their experience with the Wassermann reaction in syphilis. Despite frequent references chiefly in former literature as to the similarities between syphilis and tuberculosis they are entirely and fundamentally different: and many reasons could be advanced to show that the experiences and results of the Wassermann test should not be applied as a means of judging the practical value of serial serological tests with tuberculosis.

We have chosen a few illustrations among the clinically tuberculous (confined to the group of 50) to show how varied the serological graph may be in each individual case, and in table 1 have condensed all these to a percentage of positive results of the tests for two groups of cases and a control group. As already stated, this means of measurement cannot be regarded as exact. The variations found in each individual case prevent this. We believe, however, on the data presented that any graph could be classified as either positive, questionable or negative, and that only with an occasional graph might one be in doubt as between two adjoining classifications. Our purpose in this paper is to show what practical results will be obtained by applying this serological yard-stick (admittedly not exact) to tuberculin-positive individuals (usually known contacts).

In a similar manner X-ray films could not be divided into positives and negatives, either as films or as a measurement of clinical tuberculosis. It is perhaps fatuous to say that the proper measurement of clinical tuberculosis is the function of the clinician. This is admitted in so far as the X-ray is concerned. Our desire is to put the serological graph in a relatively similar position.

Part 2

RESULTS OBTAINED WITH SERIAL SEROLOGICAL TESTS IN TUBERCULIN-POSITIVE NORMALS (CONTACTS)

By January, 1933, the total number of contacts upon whom tests had been done was 874. The total number who started as apparent normals, chiefly students, nurses, doctors and laboratory assistants, was 290.

Out of this total of 1,164[9] cases we found there were only 51 who fulfilled or nearly fulfilled the minimal requirements of 10 tests or more, had completed a period of five years' observation or more and were tuberculin positive.

We fully realize that as small a group as 51 is at first sight a meagre number upon which to base conclusions: conclusions which we believe should be taken into consideration in the efficient control of tuberculosis. We are, however, convinced that, at the present stage of our knowledge of tuberculosis in man, duration of observation is of more importance than are greater numbers under observation for short periods: and we will rely upon the cases, selected for illustration, to demonstrate this.

These 51 cases have been divided into three groups. The 1st group (26 in number) is given in table 2 (Appendix), and includes all in which we could find no grounds to suspect tuberculosis either clinically or anatomically (by which latter is meant the X-ray films were negative). Under headings which we hope are self-explanatory the salient features of observation are recorded for each of the 3 groups.[10] Many of these individuals (table 2) were either what may be called contact conscious, or were that, and, in addition, experienced a lack of good health. Otherwise they probably would not have kept themselves under observation. Graph 5 of no. 25 (D. M. E.) is selected as showing almost perfectly

[9] We wish to record our thanks to our colleague, Doctor W. E. Ogden, for placing the histories and data of his private and clinic cases at our disposal, a large number of which appear in this group.

[10] The three groups are summaried in tables 2, 3 and 4, in the appendix: these details are given for those who are sufficiently interested or critical as to the essential data considered in the analysis of each individual.

normal serological results; perfectly normal as far as the inhibitive test is concerned and showing but 4 slight variations from normal as far as the T. C. F. is concerned.

The second group (9 in number) is given in table 3, and includes all those in whom tuberculosis could not be excluded, although no positive evidence (either a positive sputum or a positive X-ray) was obtained. Graph 6 of no. 1. (M. A. K.) is selected for illustration. This man was closely exposed to an open case of tuberculosis in 1922. While all X-rays might be regarded as suspicious, and while the graph is of the positive type, no positive evidence of tuberculosis has been obtained.

The third group (16 in number) is given in table 4, and includes all those in whom tubercle was eventually demonstrated. From this group three illustrations are selected. The first (graph 7) is no. 12 in table 4. He is chosen as showing the longest "incubation period" (12 years) from intimate contact to the demonstration of disease in a minor. He had been exposed for about two years when he was first seen at 12 years of age. The second example (graph 8) is no. 13, table 4. This shows the longest period from open contact about 1897 or 1898 till the demonstration of disease in 1931. The history and data would suggest that it illustrates reinfection from within. The third example (graph 9) is no. 14, table 4. This shows the shortest period from a change in a normal graph till the demonstration of disease in an adult. The subapical opacity which was not present in 1919 was found in 1930 about two years after the graph began to show variation from normal. In contrast to the preceding illustration the graph suggests that it demonstrates reinfection from without.

These three chosen for illustration (table 4) are by far the most dramatic or unusual, and naturally our interpretations with reference to reinfection from within (endogenous) or without (exogenous) may be questioned. However without the serological graphs we can see no indication from the remaining data as to how they could be classified with regard to their type of reinfection. This, despite the fact that tuberculin positiveness had been established from the beginning of the observations.

The majority of the remaining cases (table 4) are not especially unusual, though at the time of an established diagnosis they may have seemed so to us. They might have been detected by routine periodical examination, had the routine been persisted with for a sufficient period of time. Such persistence, however, seems doubtful to us without the stimulus provided by the graph.

The very brief summaries for these selected cases are enlarged upon in the individual histories accompanying graphs 5 to 9.

TABLE 5

Contacts under observation for 5 years or more
Correlation of clinical classification with serological graphs

CLASSIFICATION WITH REGARD TO EVIDENCE OF CLINICAL TUBERCULOSIS	NUMBER OF INDIVIDUALS	NUMBER OF TESTS	CHARACTER OF GRAPH REGARDED AS		
			Positive	Questionable	Negative
I. Positive evidence of tuberculosis	16	223	14	2	0
II. Questionable evidence of tuberculosis	9	81	3	6	0
III. No evidence of tuberculosis	26	234	2	10	14
Totals	51	538	19	18	14

Summary: (1) 16 cases eventually showed positive evidence (radiological or bacteriological) of tubercle out of a total of 37 individuals giving either a positive or questionable graph (over 43 per cent). (2) No case developed demonstrable tubercle without showing a positive or questionable graph.

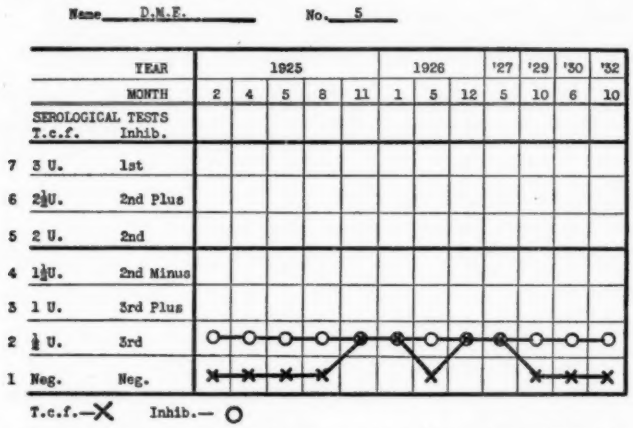
Analysis of Table 5: In the 1st column (upright) the 51 cases are divided into 3 groups, as regards the clinical evidence of tuberculosis,—decided positively only if *B. tuberculosis* was demonstrated or if there developed a positive X-ray opacity. Opposite each of these groups the number of individuals are recorded and also the number of tests. Each serological graph is there considered and recorded as positive, questionable or negative, and the totals for each group recorded. (The percentage of positive tests for each individual is shown in tables 2, 3, and 4 in the appendix.)

The summary shows two chief observations: *1:* The total number of individuals who gave either a positive or questionable graph is 37. Of this number *clinical tuberculosis became demonstrable at some time after the initial observation in 16, or in a percentage of* over 43. *2:* None of the cases developing tuberculosis gave a negative graph or, in other words, for all in whom *tuberculosis did develop some warning of this event was given by the preceding serological results.* As can be seen none of either the positive or questionable cases (clinical) gave a negative graph. Of the cases in which there were no grounds to suspect clinical disease 14, or over 50 per cent, did give a negative graph.

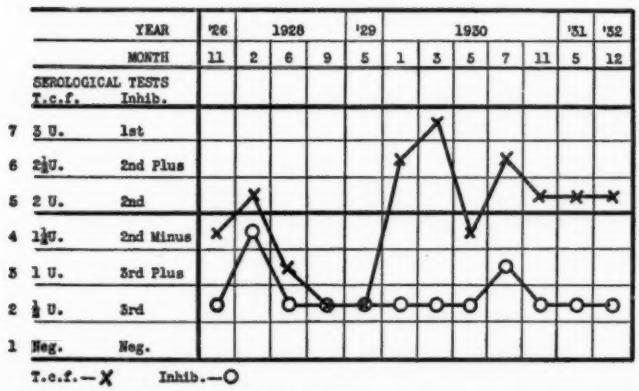
We regard the development of demonstrable disease in 43 per cent of our "serological suspects" as high, and obtained in our limited group probably because of the long duration of observation in several of the cases. In any group it would undoubtedly vary according to those many and variable factors known to be of importance in inducing the clinical outbreak.

We have felt that the value of serological graphs with tuberculin positives

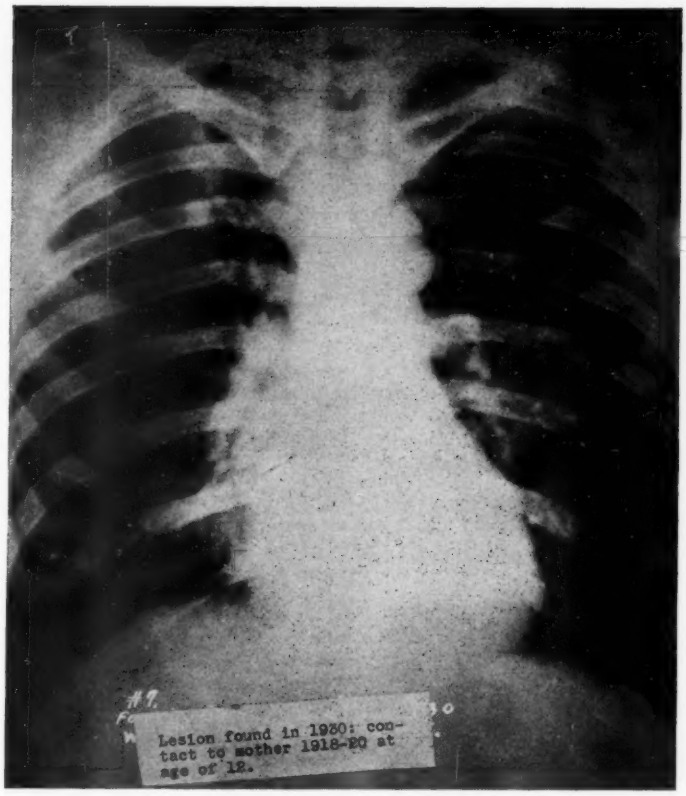
would probably be more quickly demonstrated in those exposed to silica dusts than with any other group. Unfortunately the few so exposed in which we have been able to use the tests failed to conform to the duration which we felt necessary to apply in this paper.


Name D.M.E. No. 5
YEAR 1925 1926 '27 '29 '30 '32
MONTH 2 4 5 8 11 1 5 12 5 10 6 10
SEROLOGICAL TESTS
T.c.f. Inhib.
7 3 U. 1st
6 2½U. 2nd Plus
5 2 U. 2nd
4 1½U. 2nd Minus
3 1 U. 3rd Plus
2 ½ U. 3rd
1 Neg. Neg.
T.c.f.—X Inhib.— O

GRAPH 5. (A serological graph.) D. M. E., no. 25, table 1, shows the serological findings in a tuberculin positive adult exposed to an open case of tuberculosis as a room contact. Tubercle was not regarded as bearing any relationship to any departure from health. The graph is a particularly good example of what a normal graph should be.


Name M.A.K. No. 6
YEAR '26 1928 '29 1930 '31 '32
MONTH 11 2 6 9 5 1 3 5 7 11 5 12
SEROLOGICAL TESTS
T.c.f. Inhib.
7 3 U. 1st
6 2½U. 2nd Plus
5 2 U. 2nd
4 1½U. 2nd Minus
3 1 U. 3rd Plus
2 ½ U. 3rd
1 Neg. Neg.
T.c.f.—X Inhib.—O

GRAPH 6. (A serological graph.) M. A. K., no. 1, table 2, was a contact (when in his 'teens) in 1922 to his financée, an open case of tuberculosis. He started as a normal—a student in medicine in 1926. After he was found to be tuberculin-positive and had given the initial serological tests, the history of contact was discovered. During 1930 especially he experienced considerable malaise and the thermometer occasionally registered slight fractions above 99°F. He was, however, able to continue with his duties as an interne in a general hospital (T. C. H.). No other cause has been discovered for his slight departure from good health. An unusual number of X-rays have been taken without showing any definite variation from the original and somewhat suggestive findings.



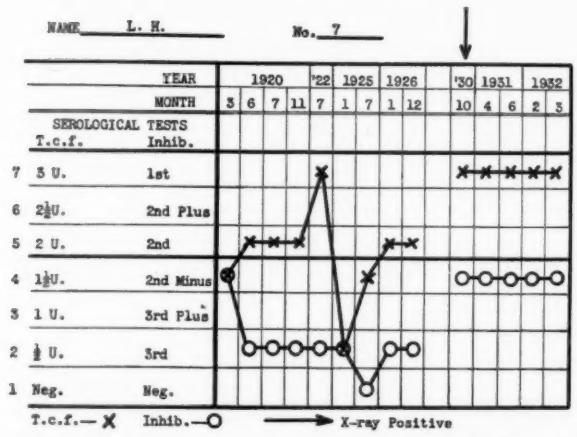
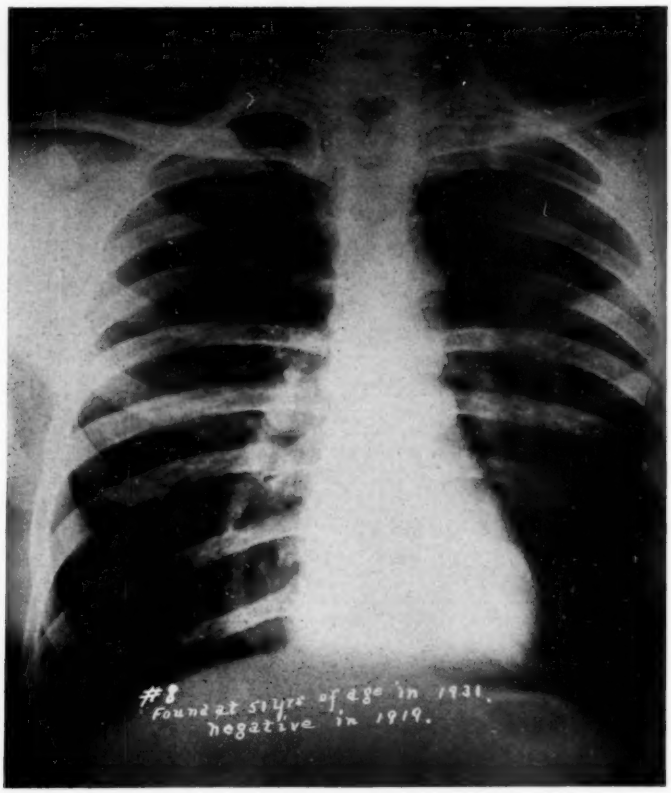


FIG. 7 AND GRAPH 7. (A serological graph and an X-ray reproduction.) L. H., no. 12, table 3. A boy, 12 years old, had been exposed to his mother, an open case of tuberculosis, for about 2 years when first seen in 1920. At that time no positive evidence of disease could be detected and in 1924 the second X-ray showed some hilar thickening (calcificatin questionable) but no positive evidence of disease. In 1928 he seemed to be in robust health. In 1930 a marked change in the serological results led to a third X-ray. This showed widely diffused though faint opacities which were interpreted as positive. He looked well. Any change from normal in physical signs was slight. Shortly after bacilli were obtained on several tests. A short course of sanatorium treatment together with pneumothorax apparently restored his health. All of the few samples of sputum obtained since the induction of pneumothorax have been negative.



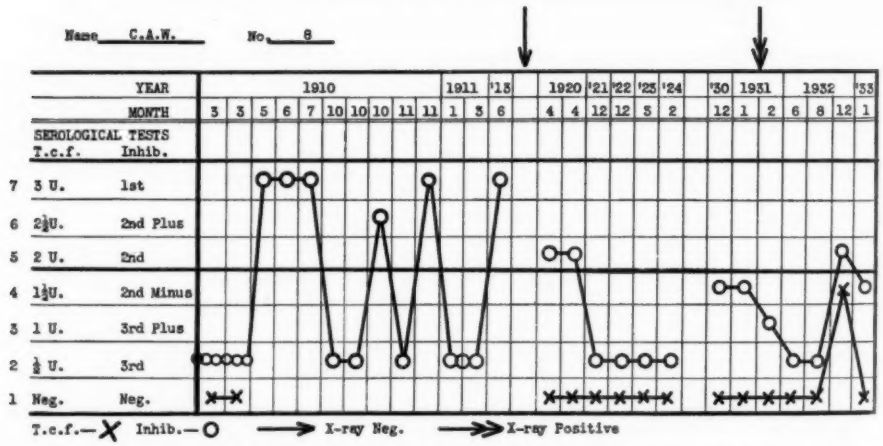
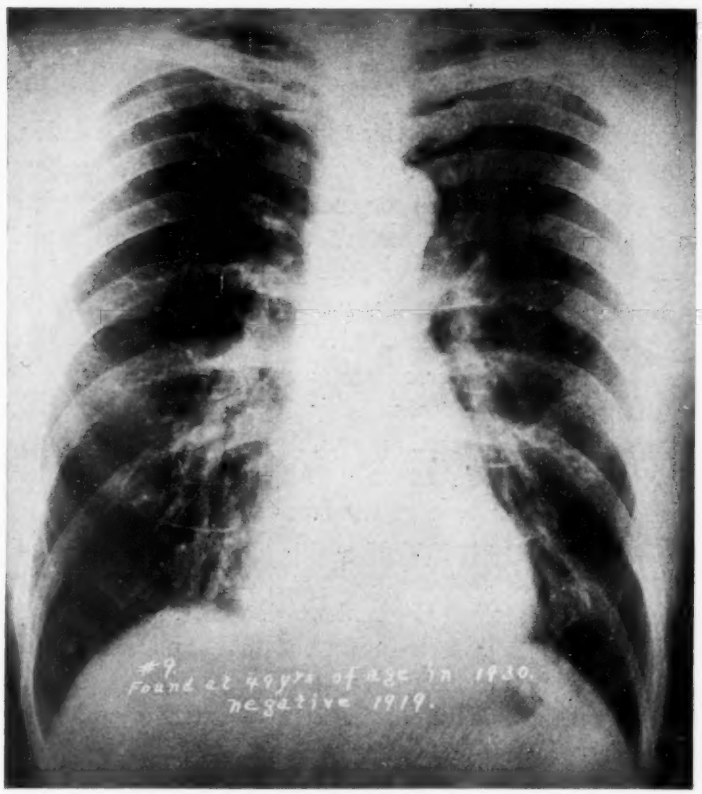


FIG. 8 AND GRAPH 8. (A serological graph and an X-ray reproduction.) C. A. W., no. 13, table 3. Was one of the earliest individuals to be tested and began as an apparent normal. Since then the following data have been assembled. The first known contact followed the diagnosis of an open case of tuberculosis in a house servant in 1897 or 1898. One other house contact developed tuberculosis of the knee. In 1909 first tuberculin skin test to 1/20 mgm. O.T. gave a local reaction of 200 x 100 mm. with vesiculation and lymphangitis. (A number of serial and quantitative tests have been carried out since then.) In 1911–12 tuberculosis of the caecum was suspected and resection advised but not carried out. At this time there was marked fatigue, slight fever and dysentery for a matter of months. In 1919 stereo X-rays showed scattered small opacities of doubtful significance. In 1930 haematuria occurred without any associated symptoms and for which no explanation was obtained. In 1931 (at the age of 51) a positive left apical lesion classified as a minimal, 2nd degree involvement, was found. On this data plus the serological results we have concluded that the reinfection came from within.



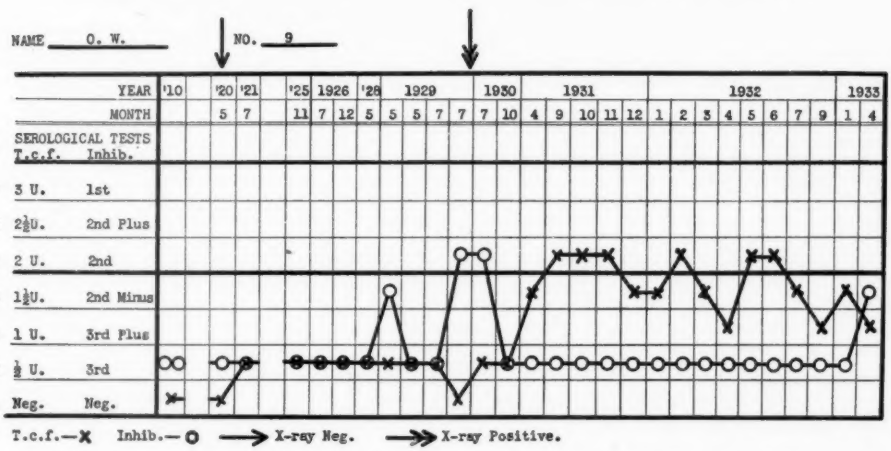

NAME O. W.
NO. 9
YEAR '10 '20 '21 '25 1926 '28 1929 1930 1931 1932 1933
MONTH 5 7 11 7 12 5 5 5 7 7 7 10 4 9 10 11 12 1 2 3 4 5 6 7 9 1 4
SEROLOGICAL TESTS
T.c.f. Inhib.
7 3 U. 1st
6 2½U. 2nd Plus
5 2 U. 2nd
4 1½U. 2nd Minus
3 1 U. 3rd Plus
2 ½ U. 3rd
1 Neg. Neg.
T.c.f.—X Inhib.—O X-ray Neg. X-ray Positive.

FIG. 9 AND GRAPH 9. (A serological graph and an X-ray reproduction.) O. W., no. 14, table 3. Was started as a tuberculin-positive in 1910, and was continued as a normal control with intermissions until 1929, when the first definite irregularity occurred. This was followed in 1930 with two more deviations from normal, when repeat films showed a positive subapical lesion in an adult aged 49. Previous films taken in 1919 were negative. Following a year's definite treatment the X-ray showed marked absorption and in the recent films can hardly be detected. On this data we have concluded that the reinfection probably came from without.

DISCUSSION

1. The purpose and scope of this paper precludes a discussion of the T. C. F. test and its application in the diagnosis of clinical tuberculosis. The inhibitive test has received so much less attention in the literature and is so relatively unknown that a few further remarks would seem applicable. A few clinicians in or close to Toronto have tried to use it and have attempted to divide their cases on the basis of one or two tests into those giving positive and negative results. Inevitably their conclusions must have been adverse from any point of view, as we hope all our illustrations show. Others, notably Perla,[11] have attempted to use the test by modifying the technique and his adverse publication was answered by Norwich and MacLennan.[12] All our colleagues who have had adequate and intimate knowledge furnished through the use of the dual serial tests have come to rely upon them.

2. Three proved and accepted methods give us cross-lights upon the stream of events which follow the implantation of *B. tuberculosis* in man. The tuberculin test with its well-known but dual implication of infection or disease, the demonstration of the presence of tubercle bacilli in excretion or tissue, and the evidence of tissue changes (chiefly pulmonary) by X-ray films. This latter for experienced observers may be clearly positive or doubtful.

The question we should like to raise is this: Have we presented sufficient data to warrant the assumption that serial serological tests provide a fourth method by means of which further light can be shed on the problems involved in tuberculous infection and disease in man? We think so; but obviously others working with the same technique must confirm our results.

3. There remains on the practical side the consideration of the examination of tuberculosis contacts. Actually the result of this yields us a percentage of individuals who are tuberculin-positive and among these a very small percentage who show a positive or questionable lesion. The contact expects to be told that he either has or has not got tuberculosis. If one cannot say there is disease his coöperation for the desired periodical examinations is materially lessened. Especially is this true if at the time

[11] Perla, D.: The inhibitive reaction of tuberculosis serum, *Amer. Rev. Tuberc.*, 1926, xiv, 706, and The inhibitive reaction of Caulfeild, *Ibid.*, xiv, 718.

[12] Norwich, MacLennan and Bassingthwaighte: The inhibitive reaction of Caulfeild, *Amer. Rev. Tuberc.*, 1930, xxi, 142.

his feeling of well-being is satisfactory. If one eliminates those showing positive or questionable lesions on the first or second examinations, one is left with the feeling that a disproportionate amount of work will be expended upon the remainder: that is, in proportion to the relative few in whom a lesion will be found in the near or distant future.

The results of the serial tests have helped us in discriminating among the tuberculin positives, those whom we feel should be kept under adequate observation. The definite knowledge that they are "serological suspects" in addition to the fact that they are tuberculin-positive undoubtedly gives one a moral support that aids in stressing the importance of maintaining the periodical examination.

This has resulted, as is shown in table 5, in the definite detection of clinical tuberculosis in an early stage in over 43 per cent of those regarded as needing this close attention. Of the 16 cases so detected two died—extension of the disease taking place *after* the diagnosis; one developed a sudden tuberculous pneumonia *after* the diagnosis; one is on pneumothorax and working. With the remainder, tubercle is now of relatively minor or of no importance in so far as their health is concerned. (See table 4, Appendix.) This we consider a very practical result which it would be impossible to obtain by any other method.

The remainder of those classed as serological suspects and in consequence needing continued periodical observation total 21. To what extent our admonitions regarding their type of life helped prevent the development of clinical disease can of course be only speculative. We believe we did accomplish this to an unknown and unprovable extent. Likewise to an unknown extent the graphs were possibly "false positives."

It is regrettable that out of over 1,000 cases examined and tested we have only 51 who were tuberculin-positive, and fulfilled, or nearly so, the minimal requirements as regards duration and the number of tests. It has become plain to us that satisfactory numbers can only be obtained by a well-organized field and follow-up service. It is our hope that the results reported in this paper may stimulate such an endeavor. The reasons for insisting upon a prolonged duration and about 10 tests are we believe amply demonstrated by the cases chosen for illustration.

SUMMARY

1. As a result of prolonged observation on cases of clinical tuberculosis in which dual serial serological tests had been taken we have struck an average from the number of positive tests obtained. Each graph is

about as individualistic as each case is clinically individualistic and as a result we have obtained an inexact yard-stick.

2. An average of positive serological results obtained in tuberculin-negative normals was struck as evidence of the percentage of laboratory error for the tests.

3. We have given illustrations to show that the serological graph may be similar whether the extent of pathological involvement be far advanced or minimal. The number of such illustrations could be multiplied sufficiently to show (we believe) that this is fundamental.

4. Applying this serological yard-stick to tuberculin positive individuals (most of whom were known contacts) we have shown that tubercle was finally demonstrated in over 43 per cent of those whose graph was regarded as either positive or questionable. It was also found that no case developed tuberculosis without warning of this being afforded by the preceding serological results.

5. The longest period in a minor from the initial observation, while the individual was under contact, to the demonstration of disease was 12 years (graph 7); the longest period in an adult from the first positive tuberculin test was 22 years (graph 8); the shortest period in an adult (starting as a tuberculin-positive normal) from the first positive serological test was under 2 years (graph 9).

6. While we believe dual serial serological tests have a practical application in the handling of the clinically tuberculous, we hope we have demonstrated that, from a public-health point of view, they have a distinct and more important value in enabling us to discriminate among the tuberculosis contacts (tuberculin-positive individuals) those who should be closely followed and kept under adequate periodical observation.

7. Tuberculin positiveness indicates the previous implantation of *B. tuberculosis* and the formation of anatomical tubercle. The establishment of a suggestive number of positive serological results would seem to demonstrate that the individual is on the threshold of or is actually suffering from clinical disease and should be periodically examined; the actual demonstration of bacilli or X-ray proof may take years.

We wish to record our appreciation to the Department of Pensions and National Health (Canada) for the maintenance of the Serological Laboratory. This facility has been granted because of our insistence that the results of the periodical tests have helped enormously in the diagnosis and in the assessing of the pensionable disability of the tuberculous ex-soldier. It is a matter of gratification to acknowlege also the privilege of utilizing these tests in the groups of apparent normals and contacts reported upon in this paper.

To Dr. A. C. Norwich (Clinical Pathologist to Christie St. Hospital) and his assistants,

Miss M. F. MacLennan and Miss M. Bassingthwaighte, we wish to acknowledge our thanks and appreciation of the thoroughness and the interest they have shown in carrying on with the serological work.

For the compilation of the percentages given in the charts, and for the arrangement of the charts and graphs, we wish to acknowledge the indispensable assistance and advice of Dr. R. D. Defries of the Department of Epidemiology and Biometrics, University of Toronto.

Appendix

TABLE 2

Contacts or tuberculin-positive normals in whom there were no grounds to suspect tuberculosis, either clinically or anatomically

NUMBER	CASE NUMBER OR INITIALS	YEAR OF 1ST OBSERVATION	NUMBER OF TESTS	PERCENTAGE RESULTS		CHARACTER OF GRAPH	REMARKS
				Pos. T.C.F.	Pos. Inhib.		
1	D. A. G.	1921	8	10	0	Neg.	
2	R. A. G.	1921	9	5	0	Neg.	Never strong; no definite cause found
3	C. C.	1920	10	90	0	Pos. (?)	
4	McC.	1923	9	0	33	? (Pos.).	
5	J. S.	1924	10	11	5	?	
6	Sieb.	1921	8	44	19	Pos.	
7	Smar.	1923	9	19	0	Neg.	
8	C. W.	1925	8	0	0	Neg.	
9	R. C. W.	1927	10	5	0	Neg.	
10	R. C.	1925	10	0	0	Neg.	
11	Fara	1927	8	6	6	?	
12	M. F.	1920	9	12	0	Neg.	
13	E. H.	1926	9	0	0	Neg.	
14	Hocken.	1924	10	0	0	Neg.	
15	M. K.	1927	9	0	0	Neg.	
16	M. 17739	1928	8	0	14	?	
17	C. 17142	1928	7	25	8	?	
18	G. 18684	1928	7	50	0	?	
19	S. 21954	1928	8	0	0	Neg.	
20	L. 7447	1925	7	43	0	Neg. (?)	
21	Mc. 28109	1925	11	4	0	Neg.	
22	H. Mc.	1925	12	42	0	? (Neg.)	
23	E. R. 3842	1923	18	34	3	?	
24	R. G.	1924	9	33	0	?	
25	D. M. E.	1925	12	0	0	Neg.	
26	M. B.	1926	9	0	0	Neg.	Developed from Tbn.-neg. to pos. during observation

TABLE 3

Contacts or tuberculin-positive normals in whom tuberculosis was not excluded

NUMBER	CASE NUMBER OR INITIALS	YEAR OF 1ST OBSERVATION	NUMBER OF TESTS	PERCENTAGE RESULTS		CHARACTER OF GRAPH	REMARKS
				Pos. T.C.F.	Pos. Inhib.		
1	M. A. K.	1924	12	67	4	Pos.	Contact to fiancée 1920: X-rays subminimal or suspicious; working
2	S. V.	1926	8	50	0	?	X-ray subminimal*
3	True.	1927	8	0	15	?	X-ray subminimal
4	Cripp.	1927	8	42	0	?	X-ray subminimal
5	C. 20764	1928	8	50	0	?	X-ray subminimal
6	C. 20763	1928	8	100	14	Pos.	X-ray subminimal
7	C. 14048	1927	10	15	0	?	X-ray subminimal
8	14052	1926	9	43	0	?	X-ray subminimal
9	W. H. S.	1928	10	100	5	Pos.	X-ray subminimal. Last two years in perfect health, in contrast to previous experience

* In certain of these cases other conditions of nontuberculous aetiology have been found.

TABLE 4

Contacts or tuberculin-positive normals developing positive lesions while under observation

NUMBER	CASE NUMBER OR INITIALS	YEAR OF 1ST OBSERVATION	NUMBER OF TESTS	PERCENTAGE RESULTS		CHARACTER OF GRAPH	SPUTUM	LAST X-RAY	REMARKS
				Pos. T.C.F.	Pos. Inhib.				
1	12841	1926	12	70	4	Pos.		M. A.	Working, well
2	3845	1923	12	37	8	Pos.		M. A.	Developed sudden tuberculous pneumonia
3	7125	1925	22	27	4	Pos.		M^2	Working
4	10303	1925	8	31	12	Pos.	Pos.	M. A.	Discharged from Sanatorium 1930. Condition in December, 1932 relatively good
5	21945	1927	8	31	0	?	Pos.	M^2	Contact to wife who died April, 1930. Now in Sanatorium
6	4918	1924	7	93	0	Pos.		M^1	Married and well
7	R. E.	1921	7	7	15	Pos.		M^1	Apparent cure: recent accidental death
8	S. M.	1924	9	45	10	Pos.		M^1	Apparent cure
9	W. S.	1924	7	29	0	?		M^2	Apparent cure
10	Fid.	1926	9	0	14	Pos.	Pos.	M. A.	Developed acute flare-up. Died March, 1933
11	H. C.	1926	23	4	48	Pos.		M^2	Contact to wife in mid-adult age; working; app. cure
12	L. H.	1920	14	86	28	Pos.	Pos.	M^2	Working; on pneumothorax; contact to mother as minor
13 NC	C. A. W.	1910	32	2	32	Pos.		M^2	Working
14 N	O. W.	1910	29	31	8	Pos.		M^2	Working; X-ray opacity cleared in 1½ years
15 NC	T. H. F.	1921	8	56	6	Pos.		M^1	Worked throughout; contact to father discovered afterward
16	M. L.	1925	17	55	14	Pos.		M^2	Working

N: Started as a tuberculin-positive normal.

NC: Started as a tuberculin-positive normal, and contact subsequently discovered.

M^1 = minimal first degree; M^2 = minimal second degree; M.A. = moderately advanced. (CAULFEILD and RICHARDS: *The systematic study and classification of stereograms of the chest, Canadian Med. Assn. J., 1927, xvii, 794.*)

CARBON DIOXIDE INHALATION IN PULMONARY TUBERCULOSIS[1,2]

ANDREW L. BANYAI

The attempt to use inhalations of a mixture of carbon dioxide and oxygen for the alleviation of cough and dyspnoea in pulmonary tuberculosis was based on the pioneer work of Henderson (1), and Henderson, Haggard, and their associates (2). They found that such inhalations have a highly beneficial effect following general anaesthesia in that an augmentation of breathing was caused which rapidly ventilated the anaesthetic out of the blood, and it also acted as a powerful stimulant on the circulation, particularly on the venous return. It has been used for the prevention and overcoming of massive atelectasis, for resuscitation from carbon-monoxide poisoning, from ether and alcoholic intoxication, from respiratory failure due to other causes, such as morphine poisoning, and for the resuscitation of newborn infants.

It was found by Henderson (1) that when a man or an animal is exposed to a deficiency of oxygen for a time, his breathing is greatly augmented and he blows off more carbon dioxide than the body can well afford. Such a deficiency of carbon dioxide leads to a respiratory failure which not only cannot be corrected by the administration of oxygen but is made worse by it. He says:

> We know that the stimulant which nature herself uses to maintain breathing is carbon dioxide. It is the increased production of carbon dioxide during muscular exercise that causes the corresponding increase in the volume of air breathed. It thus provides the increased supply of oxygen to meet the increased need. Conversely, if the carbon dioxide in the blood is abnormally decreased by excessive breathing, we know from well-established experiments that respiration is liable to stop until the normal amount of carbon dioxide reaccumulates in the blood and again stimulates the respiratory system.

Furthermore, he states that "oxygen deficiency, if at all intense, acts as a sort of whip, which excites respiration to activity, and even to excessive

[1] From Muirdale Sanatorium, Wauwatosa, Wisconsin.

[2] Presented at the thirtieth annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, May 15, 1934.

activity, but injures at the same time and is liable to be followed by a subsequent period of depressed breathing."

Extensive parenchymal lesions, particularly multiple bronchopneumonic and pneumonic processes are often responsible for an increased respiratory rate and various degrees of dyspnoea during the course of pulmonary tuberculosis. The accumulation and retention of mucopurulent secretion in the alveoli and bronchi are frequently conducive to shortness of breath in debilitated tuberculosis patients, in whom, because of pathological changes in the bronchial tract, or because of the weakness and exhaustion of the respiratory muscles, the expectoration is inadequate. Massive atelectasis, although not often seen in tuberculosis, causes varying degrees of dyspnoea. The intensity of this symptom depends on the suddenness of the development of atelectasis. Furthermore, we believe that multiple lobular atelectasis, which causes a loss of a part of the respiratory surface, and may increase the respiratory rate, and because of its insufficient blood-supply may serve as a predilectional place for the development of new, metastatic tuberculous foci, is more common in widespread pulmonary tuberculosis than it is generally realized. The obstruction of bronchi by tuberculous bronchitis, inflammatory oedema of the bronchial wall, by large cavities, or by a mucous plug, obliteration by a tuberculous infiltration of blood-vessels supplying lobules, occlusion of blood-vessels by endarteritis or by toxic thrombosis are liable to cause lobular atelectasis. Smaller or larger atelectatic areas at the margins and the bases of the lungs are frequently found in cases in which the respiratory movements are restricted because of thoracic pain, adhesions, or fear of haemorrhage, and also in cachectic persons.

Severe cough interferes with the rest of the patient and with the rest of the lungs, which is the basic feature of the treatment of tuberculosis. It may also cause the spread of the disease from one part of the lung to the other, or from one lung to the other. Excessive cough may accelerate the development of tuberculous laryngitis, emphysema, and spontaneous pneumothorax, or lead to haemorrhage, also to vomiting, loss of appetite, exhaustion, headache, insomnia, rise in temperature, marked dyspnoea, cyanosis, thoracic pain, subconjunctival haemorrhage, or to urinary incontinence.

On the other hand, there is the necessity of removing accumulated secretion from the bronchial system to establish a free passage of air to and from the alveoli and to maintain a normal oxygen-carbon-dioxide exchange in the lungs.

A failure to get the desired results from the generally accepted cough sedatives, expectorants and related medication was met with in patients in whom we used carbon-dioxide inhalations subsequently. The administration of carbon-dioxide-oxygen was followed by gratifying results in the great majority of these cases. A. Lincoln Brown (3) succeeded in making observations through a bronchoscope during carbon-dioxide-oxygen inhalation in postoperative atelectasis. His findings were summarized as follows: (1) There is an increase in the rate and depth of breathing; (2) by the increase of depth of breathing the walls of the bronchi are caused to approximate one another, and in this manner tend to free any secretion attached to the wall; (3) blanching of the mucous membrane. Similar findings were reported by Brunn and Brill (4).

The importance of the restoration of the normal respiratory depth or its increase is well appreciable from the studies of Van Allen and his associates (5) who pointed out that coughing cannot be effective unless the lungs are well inflated.

Prinzmetal and his co-workers (6) found that the inhalation of 10 per cent carbon dioxide caused an increase in the circumference of the chest and in the negativity of the intrapleural pressure, which, in turn, tends to pull out atelectatic areas. They also reported that not only the inspiration but the expiration becomes more forceful during carbon-dioxide inhalation.

Technique: The apparatus used in our work consists of a tank, containing a mixture of 10 per cent carbon dioxide and 90 per cent oxygen, with an oxymeter which regulates the flow of gas per minute; and an inhaler is connected to the tank by a rubber tubing. A rubber bag, which serves as a small reservoir, is attached to the rubber tubing by means of a T-tube. The oxymeter is set for from 5 to 7 litres per minute, depending upon the individual reaction. Herxheimer and Kost (7) found less response, when carbon dioxide was given in slowly and gradually increased concentrations, than following the direct administration of the same concentration of the gas. The patient may be seated on a chair or kept in his bed. The purpose of the procedure is explained to the patient to remove fear of general anaesthesia or some surgical operation. In some persons who seemed alarmed, we found it more expedient to use a glass tube instead of the inhaler. The patient was instructed to hold the end of the glass tube in his mouth, to inhale the gas mixture coming from the tank and to exhale through the nose. Although the admixture

of air with and dilution of the inhaled gas was unavoidable by this procedure, the effect seemed to be quite satisfactory. This open inhalation is also recommended when the patient's general condition is weak, and

FIG. 1. Apparatus for carbon-dioxide-oxygen inhalations. The gauge, which indicates the flow of the mixture in litres per minute, is connected to the pressure-reducing regulator, manufactured by the Heidbrink Co., Minneapolis. The face mask can be removed, and a glass tube used as a mouthpiece.

for cases in which disagreeable subjective symptoms are noticed when the closed inhaler is employed.

At the beginning of this investigation, the length of the first inhalation was limited to 3–5 minutes. This was increased to 10 minutes on the

second day and to 15 minutes on the third day. From then on inhalations were given for the same length of time. We found that most patients tolerated well 15-minute inhalations, given through a glass tube; therefore, the length of the initial inhalation by this method was set to 15 minutes and continued with the same length of time. In one patient, the inhalations were given for 30 minutes on two successive days with gratifying results and without any disagreeable consequences. The length of treatments was limited to 10 minutes when the closed inhaler was used. It is good practice to let the patient discontinue the inhalation for 1–2 minutes following each three-minute inhalation. Thus we preclude the occurrence of fatigue, discomfort, or other disagreeable symptoms. It was observed that in some patients, who readily responded to 15-minute inhalations in the beginning, the length of treatment could be reduced to 10 minutes during the later course without losing any of its effectiveness.

We believe that the best policy in the use of this procedure should be the same as in the administration of any other drug. The dosage should be adapted to the individual case. *The amount of carbon dioxide given must be the minimum dose, which is sufficient to produce the necessary increase in the peristalsis of the bronchi and to induce a gradual expansion and aeration of the occluded, atelectatic portions of the lung.*

The number of inhalations varied from 1 to 20. The treatments were given on successive days or at few days' intervals. The intervals should be arranged according to the duration of the relief obtained. For prolonged treatment two inhalations a week, three days apart, were found most satisfactory.

Observations: The effect of carbon-dioxide-oxygen inhalations was analyzed in 50 cases of pulmonary tuberculosis. Shortly after the beginning of inhalations, usually within the first minute, the increased respiratory action became evident. With each inspiration, the patient appeared as if taking a deep breath. The increase of the chest circumference was noticeable with each inspiration and was in obvious contrast with the shallow breathing prior to the inhalation. The patients, as a rule, appeared to be comfortable and relieved.

The rate of respirations varied greatly during inhalations not only in different individuals but also in the same individual on successive days. In some patients there was a rather sudden drop (in one instance from 26 to 10, in two minutes), while in others a decrease in the respiratory rate

came on gradually. Still in others an initial drop was followed by a rise to the usual level. An increase in the respiratory rate from the beginning of the inhalations was noted in several patients. All these changes were restored to the rate recorded prior to the treatment, a few minutes after the inhalations were stopped.

Carbon-dioxide inhalation caused a moderate rise in the blood-pressure in the majority of cases in which such measurements were made before, during and after the treatment. This is attributed to the contraction of the peripheral, particularly the splanchnic vessels (8).

The most striking subjective response consists of the chest feeling lighter and respiration being easier. Remarks that "it felt like it would clear the chest," or "the lungs were clear after inhalation," or "as it opened up the air pipes," or "it feels like there is more room in the chest to breathe" were often made by the patients when questioned about their subjective feeling after treatments. Immediate relief from a sensation of pressure and heaviness in the chest was reported by several patients.

The most consistent benefit was that expectoration became easier and consequently the cough decreased. Spells of exhaustive, "dry," unproductive cough were followed by an almost effortless expectoration. The amount of sputum thus evacuated from the lungs was rather surprising to the patients and to ourselves. Following such copious expectorations, cough naturally was absent for several hours. We have estimated that in some instances the cough became at least 50 per cent less than prior to the treatment. In others, the cough appeared at certain periods instead of the continuous coughing they were previously suffering with.

We have observed a change of the character of the sputum from a heavy, thick and tenacious type into a thinner, serous, and more watery kind. In one instance a purulent, greenish somewhat foetid sputum changed into a more serous type and lost its odor.

Besides the fact that exertion on coughing was prevented, the removal of large amounts of accumulated inflammatory products from the lungs and the possible release of patchy atelectatic areas lead to the relief from dyspnoea. It was noticeable that the patients' breathing eased up and that they were able to move around with more comfort and less shortness of breath than before. The easier and more effective expectoration, the lessening of fatiguing cough, and the relief from dyspnoea were conducive to better, more quiet, and relaxed sleep and thus indirectly to more rest and to an improvement of the general subjective feeling.

The improved appetite of some of these patients must be considered also as an indirect result of the treatment. Other incidental benefits were the relief from throat discomfort in 3 patients who had laryngeal tuberculosis and the fact that they could lie on both sides which had been difficult because of shortness of breath before, and the disappearance of chest noises. The relief obtained in laryngeal cases may be explained as due to the elimination of excessive irritation by continuous coughing.

Full benefits of the treatment were noticeable in some of the patients only after the third or fourth day of the inhalations. The relief from heaviness in the chest lasted from one hour to two days. Easier expectoration, decrease in cough, and relief from dyspnoea, together with their consequent general effects, lasted from one day to 4 weeks, following the average course of treatment of 10 inhalations. Naturally, just as the immediate symptomatic improvement showed individual variations in uniformity and degree, so there were considerable differences in the duration of benefits obtained.

No benefits were noticed, subjectively or objectively, in 5 cases. Two of this group had one inhalation only and refused further treatment. One patient with a widespread pulmonary tuberculosis had attacks of coughing, the source of which was presumably a sclerotic contraction of the previously tuberculous larynx. The remaining two patients had extensive pulmonary tuberculosis which was complicated by tuberculous laryngitis in one of them. The latter patient was in a preterminal condition at the time of treatment.

Complaints during the treatment were of minor significance and attributable to symptoms of a transient character: weakness in 2, slight shaky feeling in 4, hot sensations in 3, frontal headache in 6, palpitation in 7, and slight dizziness in 8 cases. The development of these symptoms was, however, limited to a small fraction of the number of inhalations given in the individual case. Some patients had more than one of these symptoms.

Indications: 1: Strenuous, exhaustive cough without effective expectoration: (a) if there is evidence of inflammatory exudation in the lungs; (b) when the cough is insufficient to evacuate sticky, thick sputum, and thereby causes gagging, vomiting, incontinence, etc.; (c) when the sleep and rest of the patient are disturbed by coughing during the night. The inhalations should not be given if the source of the cough is outside of the lungs, such as laryngitis, pleurisy with or without effusion, cardiac de

compensation, etc. *2:* Dyspnoea originating from multiple lobular atelectasis. The frequency of this condition deserves particular emphasis. We wish to refer to the survey of Korol (9) who quotes the works of several investigators which deal with atelectasis complicating pulmonary tuberculosis. It was found that the bronchi are frequently invaded and occluded by the tuberculous process. Chronic fibroid tuberculosis as well as caseous bronchitis, mucous secretion or a blood clot may be the source of atelectasis of a lobe or several lobules. *3:* Dyspnoea originating from massive atelectasis, the latter being characterized by contraction of the affected side, displacement of the diaphragm and mediastinal structures toward the atelectatic area, impaired percussion note and feeble breath-sounds. The signs are proportionate with the degree of atelectasis. This indication is based on the fundamental works of Henderson and his associates (2) and on the experimental studies of Coryllos and Birnbaum (10), which have been followed by a widespread use of carbon dioxide for the prevention and treatment of this condition in non-tuberculous individuals. *4:* Presence of large cavities communicating with a bronchus, without sufficient drainage from the cavity. *5:* Bronchiectasis secondary to a pulmonary fibrosis associated with the healing process, when postural drainage is not effective in evacuating the secretion from the dilated bronchi. *6:* For aiding expectoration in cases of retention of inflammatory products following phrenic-nerve block or during the course of artificial pneumothorax. *7:* Cough which is not strenuous, but is not sufficient to remove accumulated material from the lungs. Prevention or elimination of such a retention may obviate the absorption of toxins and may correct toxic symptoms, and induce a return to normal temperature, even if only temporarily. *8:* Aiding re-expansion of the collapsed lung following drainage for empyema as recommended by Churchill (11).

Contraindications: 1: Haemorrhagic tendencies, because of a possible risk of inducing haemorrhage by increased respiratory expansion. Fuchs (12) found that, while a small increase in the blood carbon dioxide increases its coagulability, too much carbon dioxide in the plasma causes prolonged coagulation. *2:* Superficial, thin-walled cavities, because of the possibility of rupture and causing a pneumothorax. *3:* Marked emphysema. *4:* Widespread pulmonary fibrosis without atelectasis and without mucopurulent retention in the air-passages. *5:* Acute plastic pleurisy and pleural effusion. *6:* Hypertension. *7:* When the cause of dyspnoea or cough is outside of the lungs. *8:* Extreme general debility.

Discussion: The beneficial results reported in this study are attributed to the effect of carbon dioxide as a respiratory stimulant. We consider carbon dioxide (10 per cent carbon dioxide and 90 per cent oxygen) *an ideal remedy for the removal of thick, sticky mucous secretion from the lower respiratory passages.* The inhalations are followed by an easy, effortless, often almost coughless, drainage of the lungs. Such a greatly facilitated evacuation of the bronchial system not only protects the patient from undue physical exhaustion during spells of strenuous cough, but they also ensure restful intervals between periods of expectoration. The relief from heaviness over the chest following inhalations must be, at least partly, attributed to the elimination of multiple lobular atelectasis. This, in turn, aids the effective inflation of the lung, which is necessary for the clearing of the bronchi of accumulated mucus. It is also probable that the improved blood circulation of the reinflated atelectatic areas aids expectoration. The rest and comfort which follows these treatments and the subsequent ameliorated expectoration is worth the effort and time spent with it.

The symptomatic relief observed in these cases suggested the thought that some other factor besides that already mentioned, particularly the presence of oxygen (90 per cent) in the gas mixture, might play a rôle in the results obtained.

It is problematical whether other properties of carbon dioxide have any importance when it is used by the inhalational method. Observations and experiments related to this subject might be of some interest. It has been noted by clinicians that patients with certain types of heart disease, which cause a long-standing passive congestion of the lung, suffer only rarely with active pulmonary tuberculosis. The antagonism between diseases of the heart which produce a passive hyperaemia in the lung and pulmonary tuberculosis was first emphasized by Rokitansky (13) in 1844. His postulate that heart disease with consequent passive engorgement of the lungs is a preventive of tuberculosis in the same organ was corroborated by other investigators on clinical material, as well as on postmortem studies. Osler (14) found that mitral stenosis has a marked inhibitory effect on tuberculosis. Fishberg (15) says that, although tuberculous *infection* occurs in these cases as frequently as in the general population, *active and progressive* tuberculosis is prevented by the congestion and plethora of the lesser circulation. The relative infrequency of pulmonary tuberculosis in atrophic emphysema is ascribed by Fishberg (15) also to the venous hyperaemia of the lung. Bier advo-

cated the use of passive congestion for the treatment of orthopaedic forms of tuberculosis and reported favorable results obtained thereby.

Sewall (16) expressed the idea that passive hyperaemia may be an important aid in the cure of pulmonary tuberculosis when certain degrees of collapse are established by artificial pneumothorax. Levinson and Petersen (17) pointed out that the resistance of lungs with passive congestion to tuberculosis may be attributed to a high carbon-dioxide content, as has been demonstrated by Corper, Gauss and Rensch (18). In the conclusions of their investigation concerning the effect of carbon dioxide upon the tubercle bacillus, Corper, Gauss and Rensch state that 3 per cent carbon-dioxide causes some inhibition of the growth of the tubercle bacillus in the test-tube and that 15 per cent is tuberculocidal. Cultures of tubercle bacilli buried in the tissues of animals and permitted to acquire the carbon-dioxide concentration of the body are definitely inhibited in their growth, while other cultures similarly buried, except that the ingress of atmospheric air is permitted, show no inhibition. When viable tubercle bacilli are placed in a closed system, their growth becomes inhibited as the carbon dioxide which the organisms elaborate approaches a concentration of approximately 5.5 per cent.

These data suggest a study of the possibility of influencing pulmonary tuberculosis favorably by the inhalations of high concentrations of carbon dioxide, mixed with sufficient amounts of oxygen.

CONCLUSIONS

1. The administration of a mixture of 10 per cent carbon dioxide and 90 per cent oxygen by means of repeated inhalations was found to be a safe procedure in pulmonary tuberculosis.

2. The most consistent benefits derived from this treatment were (a) easy, effortless expectoration; (b) diminution of cough; and (c) relief from dyspnoea.

3. Concomitant beneficial results were (a) sustained rest for the diseased lungs during the absence of cough; (b) better and more relaxed sleep; (c) improvement in the general well-being; (d) better appetite, and in some cases relief from laryngeal pain.

4. The inhalation of carbon dioxide not only alleviates distressing cough but also *enables one to reduce the consumption of narcotics and expectorants in such cases.*

5. The treatment should be used only in selected cases according to the indications and contraindications described above.

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ARTIFICIAL PNEUMOTHORAX IN THE 'TEENS[1]

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It has long been the general feeling among tuberculosis specialists that tuberculosis in the 'teen age carries with it a much graver significance than it does in the older age-groups. This has particularly been the attitude as regards young women with this disease. So far as we can determine, however, there is little published work on the results obtained in this age-group following actual treatment in the sanatorium. Very reliable data are to be found in the work of Edna E. Nicholson (1) and others on mortality rates, and the statistics are consistent in that they show a very high death-rate among young women between the ages of fifteen and twenty-five as compared with men of the same age or with other groups of the population. One of our purposes therefore in this paper will be to discover possible causes for such a high mortality rate and how it may be modified or corrected.

The results of this investigation are based upon a study of all patients between the ages of 12 and 21 years hospitalized in our sanatorium during the five-year period beginning September, 1928, and ending September, 1933. The patients have been arbitrarily divided into groups: *first*, according to sex; *second*, according to ages as follows, 12 to 15 years, 16 to 19 years, and 20 to 21 years; *third*, according to the amount of disease which they showed at the time of admission, namely, minimal, moderately advanced, and far advanced; *fourth*, according to whether the disease was unilateral or bilateral at the time of admission; and *last*, according to whether the sputum was positive or negative following their period of hospitalization in the sanatorium. The patients have been classified in this manner in order to determine if possible just what influence each of these factors has upon ultimate results in the different treatment groups.

Three hundred and sixty-seven patients between twelve and twenty-one years of age have been hospitalized in the sanatorium during the

[1] Read at the thirtieth annual meeting of the National Tuberculosis Association, Cincinnati, Ohio, May 15, 1934.

[2] Waverley Hills Sanatorium, Waverley Hills, Kentucky.

five-year period mentioned above. Two hundred and sixty-seven of these are white and one hundred colored. Of the 267 white patients, 91 have received pneumothorax therapy, 74 have had phrenicectomy, and the remaining 102 patients have received routine sanatorium treatment alone. Of the 100 negro patients, 24 have been treated by means of pneumothorax, 8 with phrenicectomy, and 68 with routine sanatorium care alone. A comparison, therefore, is made of the results obtained with these three methods of treatment.

TABLE 1

End-results in 267 white and 100 negro patients between 12 and 21 years of age treated with artificial pneumothorax, phrenicectomy and routinely. Patients are divided according to sex and race

SEX	NUMBER	WORKING	ARRESTED	APPARENTLY ARRESTED	IMPROVED	UNIMPROVED	NO RECORD	DEAD
				White				
Male	69 25.8%	20 29.1%	13 19.0%	2 3.0%	13 19.0%	23 33.0%	2 3.0%	16 23.0%
Female	198 74.2%	53 26.8%	40 20.2%	10 5.1%	39 19.6%	63 31.8%	11 5.6%	35 17.7%
Total	267 100%	73 27.3%	53 20.0%	12 4.5%	52 19.4%	86 32.2%	13 4.8%	51 19.1%
				Negro				
Male	40 40%	3 7.5%	3 7.5%		3 7.5%	1 2.5%	4 10.0%	29 72.5%
Female	60 60%	4 6.7%	4 6.7%		7 11.6%	6 10.0%	4 6.7%	39 65.0%
Total	100 100%	7 7%	7 7%		10 10%	7 7%	8 8%	68 68%

Let us analyze table 1, to determine what possible effect sex has upon the ultimate outcome of the case. In the first place the most outstanding finding in the table is the large number of young women hospitalized in the institution as compared with young men. In fact, 75 per cent of the white patients in this group hospitalized during the past five years have been females. On the other hand when the end-results of treatment of the two sexes are examined it is seen that the females fared equally as well or indeed somewhat better than the males.

From the comparatively large number of white females hospitalized it might appear that the morbidity rate for females in this young group is decidedly higher than it is for males of the same age-group.

Although a dependence upon history of onset of the disease cannot be entirely relied upon it was found that the average duration of time which elapsed between the first symptom and hospitalization was 10 months for the white, and $5\frac{1}{2}$ months for the negro patients, and there was practically no difference in the time interval for males or females. This would tend to show that males and females have the same opportunity to be examined by a physician equally soon following onset of the disease. It would likewise appear that the comparatively high death-rate for young girls as reported consistently in the literature is due to a large extent at least to the failure of them to become hospitalized or properly treated. In other words, if young women are diagnosed early enough and treated properly in the sanatorium they appear to have as good a chance as boys in their age-group or indeed older individuals. In comparing the end-results of pneumothorax therapy in 161 white patients of an older average age, as published previously by one of the authors (2), with the 91 pneumothorax patients in our present young series, it is found that favorable results were obtained in 73.9 per cent of the former and 72.5 per cent of the latter. Whereas the favorable results are approximately the same in the two groups, more patients in the younger group are classified as working and arrested than in the group of older average age. Andrew Peters (3) in a report of the subcommittee on artificial pneumothorax before the American Sanatorium Association in 1933 made the statement that "age of the patient does not exert an important influence on the success or failure of pneumothorax treatment."

When we examine table 1 we find that whereas 75 per cent of the white patients hospitalized were females only 60 per cent of the negro patients were females. Again, as was the case with the white patients it is seen that the negro females fared slightly better than the males of the same age-group. It is interesting to note that the end-results from artificial-pneumothorax therapy in the 12- to 21-year age-group, hospitalized during the past five years, are considerably better than the results obtained from the same method of treatment in older negro patients. In a previous article by one of the authors (2) the results in 36 negro patients of older average age are recorded. If we compare these figures with those of our present younger group of 24 patients, we find that, whereas 72.5 per cent of the former are classified as dead and unimproved, only 54 per cent

of the latter fall in this group. Again 3, or 12.5 per cent, of our present younger group are working and arrested, whereas only 1, or 3 per cent, of the older group is working and arrested. We feel that it is important to speculate on the reasons for this big difference in results in the two small but similar series of cases. The negro has a much shorter interval between onset of symptoms and hospitalization. Frequently it is found in our institution that negroes give a history of tuberculosis dating back only one month before admission. The average in this present series is $5\frac{1}{2}$ months. Only four out of the 100 patients in this series hospitalized during the past five years have had minimal tuberculosis. Practically all therefore are advanced when we see them and the majority show rapidly progressive exudative tuberculosis. In this younger group however, several were picked up in routine school examinations or following the finding of tuberculosis in some other member of the family, and were therefore hospitalized early enough to accomplish more favorable results.

The secret of success in the treatment of both the white and negro patients of this age-group, but more particularly the negro, is to get an early diagnosis and collapse the lung by means of artificial pneumothorax *immediately*. If we wait very long in the negro our chances for arrest of the disease are very slight.

The most outstanding feature in table 1 is the difference in end-results, not in relation to the two sexes but as regards the two races. Whereas only 19 per cent of the white patients have died, 68 per cent of the negroes fall into this category. There is a much larger percentage of white patients classed as unimproved than negroes, however, the percentages being 32 and 7 respectively. This again illustrates the rapidity of the disease to a fatal termination in the negro. Only 7 per cent of the negroes are working, as compared to 27 per cent in the white group. Forty-four per cent of the white patients are arrested or improved, whereas only 17 per cent of the negroes are in this class.

Let us now refer to tables 2 and 3, which are arranged for the purpose of showing end-results in the two races according to the age-groups, 12 to 15 years, 16 to 19 years, and 20 to 21 years. In table 2 it will be seen that best results were obtained in the 12- to 15-year age-group, no matter what method of treatment was followed in the sanatorium. On the other hand with the exception of the pneumothorax group it is seen that the greatest percentage of deaths occurred in the 16- to 19-year age-groups and, in general, slightly less favorable results occurred in this group.

TABLE 2

End-results in the 267 white patients classified according to age-groups and treatment received

AGE IN YEARS	NUMBER	WORKING	ARRESTED	APPARENTLY ARRESTED	IMPROVED	UNIMPROVED	NO RECORD	DEAD
				Artificial pneumothorax				
12–15	16 17.6%	5 31.2%	5 31.2%	1 6.3%	8 50.0%	2 12.5%	0	0
16–19	48 52.7%	16 33.3%	16 33.3%	2 4.2%	16 33.3%	6 12.4%	1 2.1%	7 14.7%
20–21	27 29.7%	12 44.4%	12 44.4%	0	6 22.2%	3 11.1%	0	6 22.2%
Total	91 100%	33 36.3%	33 36.3%	3 3.3%	30 33.0%	11 12.1%	1 1.1%	13 14.2%
				Phrenicectomy				
12–15	7 9.5%	2 28.5%	1 14.3%	1 14.3%	1 14.3%	3 42.8%	1 14.3%	0
16–19	40 54.0%	6 15%	3 7.5%	1 2.5%	6 15%	25 62.5%	1 2.5%	4 10%
20–21	27 36.5%	6 22.2%	2 7.4%	1 3.7%	5 18.5%	18 66.7%	0	1 3.7%
Total	74 100%	14 18.9%	6 8.1%	3 4.1%	12 16.2%	46 62.2%	2 2.7%	5 6.7%
				Routine				
12–15	22 21.5%	7 31.8%	3 13.6%	3 13.6%	3 13.6%	10 45.7%	2 9%	1 4.5%
16–19	49 48.0%	8 16.3%	3 6.1%	3 6.1%	3 6.1%	11 22.4%	6 12.2%	23 47.1%
20–21	31 30.5%	11 35.5%	8 25.8%	0	4 12.9%	8 25.8%	2 6.5%	9 29%
Total	102 100%	26 25.5%	14 13.7%	6 5.9%	10 9.8%	29 28.4%	10 9.8%	33 32.4%

TABLE 3

End-results in the 100 negro patients classified according to age-groups and treatment received

AGE IN YEARS	NUMBER	WORKING	ARRESTED	APPARENTLY ARRESTED	IMPROVED	UNIMPROVED	NO RECORD	DEAD
				Pneumothorax				
12–15	2 8.3%							2 100%
16–19	12 50.0%	2 16.7%	2 16.7%		4 33.3%	3 25.0%		3 25.0%
20–21	10 41.7%	1 10.0%	1 10.0%		4 40.0%			5 50.0%
Total	24 100%	3 12.5%	3 12.5%		8 33.3%	3 12.5%		10 41.7%
				Phrenicectomy				
12–15	1 12.5%							1 100%
16–19	5 62.5%					2 40.0%	1 20.0%	2 40.0%
20–21	2 25.0%						1 50.0%	1 50.0%
Total	8 100%					2 25.0%	2 25.0%	4 50.0%
				Routine				
12–15	17 25.0%	3 17.6%	3 17.6%		1 5.9%	1 5.9%	2 11.8%	10 58.8%
16–19	32 47.0%	1 3.1%	1 3.1%			1 3.1%	2 6.3%	28 87.5%
20–21	19 28.0%				1 5.3%		2 10.5%	16 84.2%
Total	68 100%	4 6.0%	4 6.0%		2 3.0%	2 3.0%	6 9.0%	54 79.0%

If we consider the problem from the standpoint of age alone we might consider tuberculosis to be a more dangerous disease in this age, when the girl begins to take on the responsibilities of life,—that is, between the ages of 16 and 21 years.

It might be stated here again, however, that half of the 12- to 15-year age-group were picked up on routine examination, none of which had any noticeable symptoms at the time of examination. The earlier diagnosis and the smaller amount of disease therefore undoubtedly account largely for the better end-results in this group.

In comparing end-results in the pneumothorax, phrenicectomy and routine groups, divided according to age, we are impressed with the comparatively excellent results in the pneumothorax group. Next best results were obtained in the phrenicectomy patients and least favorable results in the routinely treated group. In the pneumothorax group 72.5 per cent were favorable, in the phrenicectomy group 28 per cent, and in the routinely treated series 30 per cent. The outstanding difference between the phrenicectomy and routine groups lies in the fact that of the former 62.6 per cent were unimproved and 6.6 per cent dead, and of the latter 26.3 per cent were unimproved and 31.2 per cent dead. This would seem to prove that phrenicectomy has a very definite place in the treatment of pulmonary tuberculosis; nevertheless, pneumothorax in this young age-group is undoubtedly in our opinion the treatment of choice, and in our institution we are using it without hesitation in the earliest of cases falling within this age. In table 3 it is difficult to draw any definite conclusions concerning the negroes of the 12- to 15-year age-group, due to the small number treated. The only three patients receiving pneumothorax and phrenicectomy in this group died. However, in the routine group best end-results are still to be found in the 12- to 15-year age-group. Not a great deal of difference is to be found in comparing end-results in the other age-groups. However, as was true with the white race, pneumothorax produces the most beneficial effect of any one of the forms of therapy as shown in the table, 46 per cent obtaining favorable results. The average length of pneumothorax treatments in the negro group was 11 months. The longest-treated patient was 3 years and the shortest less than 6 months. Practically all of the negro patients who died in the pneumothorax group did so during the first year of treatment. The average length of pneumothorax treatment in the white patient was 27 months. The longest-treated patient was over 5 years, the shortest less than 6 months. Forty-four white patients out of the ninety-

TABLE 4

End-results in the 267 white patients classsified according to amount of disease at the beginning of hospitalization and treatment received

CLASSIFICATION	NUMBER	WORKING	ARRESTED	APPARENTLY ARRESTED	IMPROVED	UNIMPROVED	NO RECORD	DEAD
				Pneumothorax				
Minimal	2 2.2%				2 100.0%			
Mod. Adv.	46 50.5%	17 37.0%	17 37.0%	3 6.5%	18 39.1%	3 6.5%	0	5 10.9%
Far Adv.	43 47.3%	16 37.2%	16 37.2%	0	10 23.3%	8 18.6%	1 2.3%	8 18.6%
Total	91 100%	33 36.3%	33 36.3%	3 3.3%	30 33.0%	11 12.1%	1 1.1%	13 14.2%
				Phrenicectomy				
Minimal	3 3.6%	2 66.7%	1 33.3%	1 33.3%		1 33.3%		
Mod. Adv.	44 60.0%	10 22.7%	5 11.3%	1 2.3%	7 16.0%	29 65.9%		2 4.5%
Far Adv.	27 36.4%	2 7.4%		1 3.7%	5 18.5%	16 59.3%	2 7.4%	3 11.1%
Total	74 100%	14 18.9%	6 8.1%	3 4.1%	12 16.2%	46 62.2%	2 2.7%	5 6.7%
				Routine				
Minimal	13 12.7%	9 69.2%	5 38.5%	4 30.8%		1 7.7%	3 23.0%	
Mod. Adv.	47 46.1%	15 31.9%	7 14.9%	2 4.3%	9 19.2%	17 36.2%	6 12.7%	6 12.7%
Far Adv.	42 41.2%	2 4.8%	2 4.8%		1 2.4%	11 26.2%	1 2.4%	27 64.2%
Total	102 100%	26 25.5%	14 13.7%	6 5.9%	10 9.8%	29 28.4%	10 9.8%	33 32.4%

TABLE 5

End-results in the 100 negro patients classified according to amount of disease at the beginning of hospitalization and treatment received

CLASSIFICATION	NUMBER	WORKING	ARRESTED	APPAR-ENTLY ARRESTED	IMPROVED	UNIM-PROVED	NO RECORD	DEAD
			Pneumothorax					
Minimal								
Mod. Adv.	11 45.8%	2 18.2%	2 18.2%		4 36.4%	1 9.0%		4 36.4%
Far Adv.	13 54.2%	1 7.7%	1 7.7%		4 30.8%	2 15.4%		6 46.1%
Total	24 100%	3 12.5%	3 12.5%		8 33.3%	3 12.5%		10 41.7%
			Phrenicectomy					
Minimal								
Mod. Adv.	2 25%						1 50.0%	1 50.0%
Far Adv.	6 75%					2 33.3%	1 16.7%	3 50.0%
Total	8 100%					2 25%	2 25%	4 50%
			Routine					
Minimal	4 6.0%	2 50.0%	1 25.0%		1 25.0%		2 50.0%	
Mod. Adv.	17 25.0%	2 11.8%	3 17.6%		1 5.9%		4 23.5%	9 53.0%
Far Adv.	47 69.0%					2 4.3%		45 95.7%
Total	68 100%	4 6.0%	4 6.0%		2 3.0%	2 3.0%	6 9.0%	54 79.0%

one treated with pneumothorax received treatment longer than 2 years. Practically all of the patients that did poorly under this form of therapy did so in the first two years of treatment.

TABLE 6

End-results in the 267 white patients classified according to whether disease was unilateral or bilateral at beginning of hospitalization

DISTRIBUTION	NUMBER	WORKING	ARRESTED	APPARENTLY ARRESTED	IMPROVED	UNIMPROVED	NO RECORD	DEAD
				Pneumothorax				
Unilateral	34 37.3%	15 44.2%	15 44.2%	2 5.9%	11 32.4%	4 11.7%		2 5.8%
Bilateral	57 62.7%	18 31.6%	18 31.6%	1 1.7%	19 33.3%	7 12.3%	1 1.7%	11 19.4%
				Phrenicectomy				
Unilateral	18 24.3%	6 33.3%	3 16.7%	1 5.5%	4 22.3%	9 50.0%	1 5.5%	
Bilateral	56 75.7%	8 14.3%	3 5.4%	2 3.7%	8 14.3%	37 66.6%	1 1.7%	5 8.3%
				Routine				
Unilateral	32 31.3%	14 43.8%	6 18.7%	5 15.6%	5 15.6%	11 34.5%	5 15.6%	
Bilateral	70 68.7%	12 17.1%	8 11.4%	1 1.4%	5 7.1%	18 25.8%	5 7.1%	33 47.2%
				Total: all groups				
Unilateral	84 31.8%	35 41.6%	24 28.7%	8 9.4%	20 23.7%	24 28.8%	6 7.1%	2 2.3%
Bilateral	183 68.2%	38 20.7%	29 15.9%	4 2.1%	32 17.5%	62 33.9%	7 3.8%	49 26.8%

It is interesting to note that all of the 8 negroes receiving phrenicectomy are classified as unimproved or dead. It is also of interest to note that only 9 per cent of the routinely treated cases are classified as arrested or improved, practically all being dead. In comparing the white and negro races (tables 2 and 3) as to end-results with reference to age the

outstanding differences are the relatively very low percentage of arrested cases and the very high percentage of deaths in the negro.

Tables 4 and 5 classify all the white and negro patients according to the amount of disease present at the time of admission and show what

TABLE 7

End-results in the 100 negro patients classified according to whether disease was unilateral or bilateral at the beginning of hospitalization

DISTRIBUTION	NUMBER	WORKING	ARRESTED	APPARENTLY ARRESTED	IMPROVED	UNIMPROVED	NO RECORD	DEAD
Pneumothorax								
Unilateral	6 25.0%				2 33.3%	1 16.7%		3 50.0%
Bilateral	18 75.0%	3 16.7%	3 16.7%		6 33.3%	2 11.1%		7 38.9%
Phrenicectomy								
Unilateral	2 25.0%						1 50.0%	1 50.0%
Bilateral	6 75.0%					2 33.3%	1 16.7%	3 50.0%
Routine								
Unilateral	19 28.0%	3 15.8%	3 15.8%		2 10.5%		6 31.7%	8 42.0%
Bilateral	49 72.0%	1 2.0%	1 2.0%			2 4.1%		46 93.9%
Total: all groups								
Unilateral	27 27.0%	3 11.1%	3 11.1%		4 14.8%	1 3.7%	7 26.0%	12 44.4%
Bilateral	73 73.0%	4 5.5%	4 5.5%		6 8.2%	6 8.2%	1 1.4%	56 76.7%

influence the degree of involvement has on the end-results, regardless of the age-group. In examining the tables it will be found that best results were obtained in the minimal groups, and least favorable results in the far-advanced groups. The differences in results obtained leave no doubt

as to the influence that the amount of disease with which a patient comes to the sanatorium has upon the future outcome of the case. This is even more clearly illustrated in the negro than it is in the white race. It might be stated at this point that at the time of admission to the sanatorium 81 per cent of the advanced cases in the white group had cavity-formation. Seventy-seven per cent of the negro patients had cavity on admission to the sanatorium. No patient classified as minimal had cavity.

If we go still a step further and divide the patients into two groups according to whether they had unilateral or bilateral disease (tables 6 and 7) upon admission to the sanatorium we are greatly impressed with the fact that only 2.3 per cent of the white patients with unilateral disease have died. Twenty-eight per cent are classified as unimproved. On the other hand 26.8 per cent of the bilateral cases admitted to the sanatorium as such have died and 33.9 per cent are classified as unimproved. These figures include all white patients, regardless of the method of treatment used. The authors are impressed with these findings and feel convinced that age of the patient plays a relatively small part in the ultimate outcome of the case. In fact we have shown that patients in this group do equally as well when hospitalized as do patients in the older group. The very important point to emphasize, as we see it, is that, as the disease advances and particularly when it becomes bilateral, the chances for a favorable outlook are small. If the patient is hospitalized early enough and pneumothorax is instituted immediately, the end-results will be infinitely better and indeed favorable.

For the negro we do not feel nearly as hopeful, not only because we do not see more than an occasional minimal case on admission, but because we are dealing with a race which reacts differently to his disease. It is a common occurrence to find on admission an acute exudative tuberculosis which spreads rapidly, becomes bilateral, and ends fatally. This helps to account for the poor results in the negroes classified as unilateral on admission as seen in the table. We do feel, however, that, as indicated in tables 5 and 7, artificial pneumothorax, when instituted as early enough and particularly before the disease becomes bilateral, will definitely benefit the patient. We feel too that tuberculosis in the negro even in the face of successful collapse may spread to the opposite lung by way of the lymphatics and it is particularly important that his lung be collapsed before any marked lymph-node involvement in the root region on the affected side takes place. We have seen fairly frequently fol-

lowing the successful collapse of a unilateral case a "sunburst" involvement spreading out from the contralateral root region, and we feel that in these cases we can reasonably rule out a bronchogenic spread. In general, therefore, the only hope for favorable end-results in the negro with tuberculosis is to get it early, while it is still unilateral and without much lymph-node involvement, and immediately collapse the lung by means of pneumothorax. This holds true not only for the age-group

TABLE 8

End-results in the 267 white patients classified according to whether the sputum was positive or negative following their period of hospitalization and at the time this investigation was made

SPUTUM	NUMBER	WORKING	ARRESTED	APPARENTLY ARRESTED	IMPROVED	UNIMPROVED	NO RECORD	DEAD
				Pneumothorax				
Positive	23 25.3%				2 8.7%	9 39.1%		12 52.2%
Negative	68 74.7%	33 48.5%	33 48.5%	3 4.4%	28 41.2%	2 2.6%	1 1.3%	1 1.3%
				Phrenicectomy				
Positive	41 55.4%					35 85.6%	1 2.4%	5 12.0%
Negative	33 44.6%	14 42.4%	6 18.2%	3 9.1%	12 36.4%	11 33.3%	1 3.0%	
				Routine				
Positive	51 50.0%					17 34.0%	1 2.0%	32 64.0%
Negative	51 50.0%	26 51.0%	14 27.4%	6 11.8%	9 17.7%	12 23.5%	9 17.7%	1 1.9%

about which we are particularly interested in this paper but also for the older age-group as well.

Chadwick and his co-workers (4) report favorable results in 53 per cent of 325 negro patients receiving collapse therapy. The majority of this series received artificial pneumothorax. In our present young series, of 24 negro patients treated by means of artificial pneumothorax, approximately 46 per cent are classified as favorable.

It is again of interest to note the effect of a positive sputum upon the outcome of the case. Tables 8 and 9 illustrate this. In these tables the patients are not classified according to whether the sputum was positive or negative at the time of admission to the sanatorium. On the other hand they are classified according to whether the sputum was positive or negative at the time this investigation was made; that is, at the present time for those patients who are living and just before death in

TABLE 9

End-results in the 100 negro patients classified according to whether the sputum was positive or negative following their period of hospitalization and at the time this investigation was made

SPUTUM	NUMBER	WORKING	ARRESTED	APPARENTLY ARRESTED	IMPROVED	UNIMPROVED	NO RECORD	DEAD
				Pneumothorax				
Positive	14 58.4%				2 14.8%	2 14.8%		10 71.4%
Negative	10 41.6%	3 30.0%	3 30.0%		6 60.0%	1 10.0%		
				Phrenicectomy				
Positive	6 75.0%					2 33.3%		4 66.7%
Negative	2 25.0%						2 100.0%	
				Routine				
Positive	50 73.5%					2 4.0%		48 96.0%
Negative	18 26.5%	4 22.2%	4 22.2%		2 11.1%		6 33.3%	6 33.3%

those who have died. If we examine the tables we find that pneumothorax was far more successful in producing a negative sputum than was phrenicectomy or routine treatment. We find also that of those patients who still had a positive sputum following treatment all fell into the classification of unimproved or dead with the exception of two in the pneumothorax group who were classified as improved. In other words less than 2 per cent, or 2 out of 115 white patients who had positive

sputa following hospitalization, were improved. On the other hand all of the favorable results were obtained in the patients having negative sputa following their period of treatment in the sanatorium. Practically the same holds true for the negro as is seen in table 9. The only favorable end-results are to be found in the patients who had negative sputum following their period of hospitalization in the sanatorium. Far fewer negroes had negative sputa following treatment, however, than was the case in the white race.

In the pneumothorax group favorable end-results also naturally depend on whether the collapse of the lung was successful or not. In the white group 14 of the 91 pneumothorax cases were unsuccessful. Thirteen of these fell in the unimproved and dead columns and all had positive sputa. In the negro group 7 of the 24 pneumothorax cases were unsuccessfully collapsed. All seven of these had positive sputa and all were classified as unimproved or dead.

The great majority of patients studied in this series have been discharged. Of the 267 white patients, 53 are still receiving treatment in the sanatorium. Of these 53 patients, 35, or 66 per cent, are classified as improved and 18, or 34 per cent, as unimproved. If we subtract our sanatorium patients from the total as seen in table 1 our total end-results for all discharged and dead patients would be as follows:

TOTAL NUMBER	WORKING	ARRESTED	APPARENTLY ARRESTED	IMPROVED	UNIMPROVED	NO RECORD	DEAD
214	73	53	12	17	68	13	51
100%	34.1%	24.8%	5.6%	8.0%	31.3%	6.1%	24.0%

Of the 100 negro patients studied only 11 are still receiving treatment in the sanatorium. Eight of these (73 per cent) are improved and 3 (27 per cent) are unimproved. The only marked changes this would have on the end-results for discharged and dead patients would be in the improved and dead columns. The improved would be changed from 10 per cent to 2.2 per cent and the dead from 68 per cent to 76 per cent. The other end-results would not be altered by more than 1 or 2 per cent.

If we consider the pneumothorax groups alone they are more greatly altered on account of the fact that the majority of patients still in the sanatorium in this group are pneumothorax patients. Of the 91 white pneumothorax patients 35, or 38.5 per cent, are still hospitalized, 28 being classified as improved and 7 as unimproved. This changes the end-results as seen in table 2 and the following results are for the discharged patients alone:

TOTAL NUMBER	WORKING	ARRESTED	APPARENTLY ARRESTED	IMPROVED	UNIMPROVED	NO RECORD	DEAD
56	33	33	3	2	4	1	13
100%	60.0%	60.0%	5.4%	3.6%	7.1%	1.7%	23.2%

Nine, or 37.5 per cent, of the negro pneumothorax group are still hospitalized. Of this number 7, or 78 per cent, are improved and 2, or 22 per cent, unimproved. The end-results in table 3 would be altered as follows to show the ultimate outcome of the discharged group:

TOTAL NUMBER	WORKING	ARRESTED	APPARENTLY ARRESTED	IMPROVED	UNIMPROVED	NO RECORD	DEAD
15	3	3	0	1	1	0	10
100%	20.0%	20.0%		6.7%	6.7%		66.6%

SUMMARY AND CONCLUSIONS

1. The results of this investigation are based upon a study of all patients between the ages of 12 and 21 years hospitalized in the sanatorium during the five-year period beginning September, 1928, and ending September, 1933. The total number comprises 267 white patients and 100 negro patients.

2. A comparison is made of results obtained in the three methods of treatment, namely, artificial pneumothorax, phrenicectomy, and routine sanatorium care. The study was also made to determine what effect the following factors might have upon ultimate results in the different treatment groups: (1) sex, (2) age of patient, (3) amount of disease at the time of admission, (4) unilateral or bilateral disease at the time of admission, (5) positive or negative sputum following their period of hospitalization in the sanatorium.

3. Although statistics generally show a much higher death-rate among young girls than among young boys and older individuals, the results in this study show that young women in their 'teens obtain just as good results when hospitalized and properly treated as do young men in their 'teens. Indeed the results of treatment in this age-group are just as favorable as they are in older individuals.

4. It is shown that the amount of disease with which an individual is admitted to the sanatorium plays a much greater rôle in determining end-results than supposed and this is particularly modified according to whether the disease is unilateral or bilateral at the time of admission.

5. When the sputum remains positive following hospitalization the

end-results are uniformly poor. On the other hand, a negative sputum following hospitalization and treatment points to success of the treatment and favorable end-results in the great majority of cases.

6. In comparing the white and negro races as to end-results, the outstanding differences regardless of the method of treatment employed are the relatively very low number of arrested cases and the very high number of deaths in the negro.

7. Artificial-pneumothorax therapy in this young age-group is by far the method of choice. If the diagnosis is made early enough and particularly before the disease becomes bilateral the chances for favorable end-results are good following immediate and successful collapse of the lung by means of artificial pneumothorax. We feel that this also holds true but to a lesser degree for the negro. His disease is more frequently exudative with lymph-node involvement in the hilum, and when this is present we feel that the chances for spread to the contralateral lung by way of the lymphatics, even in the face of a good collapse, is a possibility not to be overlooked.

We wish to thank Dr. Lawrason Brown for his helpful criticism of this paper.

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ARTIFICIAL-PNEUMOTHORAX TECHNIQUE [1,2]

KENNETH P. JONES

Tice (1) tells of one of the ancients, "Pheracus, who, believing himself hopelessly advanced with pulmonary trouble, placed himself in the forefront of battle and received a wound in the chest which opened a lung abscess and this cavity healed." It is stated that rib-resections and opening of abscesses were done by Hippocrates. Boglinus (1) in 1710 advised incision of the pleura for treatment of cavities and Berry (1) in 1726 suggested the drainage of pulmonary cavities. Still later in 1821 Carson, after observing a cure following a spontaneous pneumothorax, said (1): "It has long been my belief, that if ever this disease is to be cured, it must be accomplished by a mechanical means, or in other words by operation."

In 1882 Forlanini (1) advised inducing pneumothorax and in 1888 began the practice of this treatment with nitrogen gas. In 1898 Murphy (4), though not informed of Forlanini's work, was the American pioneer in this method of treatment. His first 5 cases showed good results, and in 1899 Lemke (1), a pupil of Murphy's, gave a partial report of 53 cases, but unfortunately died before he could finish the work. For some years there is an absence of reports, the next appearing in 1912.

Among the variations of early technique, that of Brauer (1) (3) approaches the status of a major operation. He used preoperative morphine and under local anaesthesia made an incision 5 to 7 cm. long through the skin, superficial fascia and muscles, inspected the pleura for adhesions and thrust a dull cannula with an eye on the side through the parietal pleura. This cannula was large enough to admit a small ureteral catheter and Brauer advised the injection of 500 to 1000 cc. at the first operation. Murphy (4) used a tenotomy puncture through the derma and a trocar from there to the pleura, turned on the gas before reaching the pleura so that the gas flowed freely as the trocar passed into the pleural space. Forlanini (1), without anaesthesia, introduced a small-calibre aspirating needle connected with suitable apparatus, through the intercostal space, and ascertained the pleural space by manometric readings.

[1] From the Olive View Sanatorium, Olive View, California.
[2] Read before the Trudeau Society, Los Angeles, California, May 23, 1933.

Gravesen (8) in his book on surgical chest procedures states that, given a trained hand, the question of technique or apparatus is of little moment, and yet Howson in 1929 (6) showed that different-sized manometers and needles may give confusing manometric readings. Because of these conflicting statements and because of known differences in methods, it was decided to investigate the status of pneumothorax technique.

SOURCE OF STUDY

As a source, the literature was studied, but of an abundance of articles only a few gave much attention to the apparatus and technique.

A questionnaire, prepared for the most part by Dr. Proctor, was sent to thirty chest men of long experience and located in widely separated sections of the country, thus giving geographical comparisons of technique. This form asked for statements on every point which it was felt might be standardized, such as asepsis, anaesthesia, needle-size, manometer and apparatus. It even included such points as initial filling, pressure, frequency and amount of refills which lie in the widely debatable field of individualization of the patient. These latter were not included in any attempt to standardize these procedures but simply to show general trends.

In discussing asepsis, it is desired to impress two thoughts upon the reader. The first is that most clinicians in the survey signified that infection certainly could be carried into the chest by pneumothorax treatment, and Olive View Sanatorium has experienced several skin infections in spite of what is considered sterile technique. The second thought is that our pathologist, Dr. Bogen (11), cultured air from a pneumothorax apparatus without a cotton filter and secured growths of short-chain streptococci, while the machines with filters gave negative cultures.

Examination of the literature shows that generally such aseptic technique as scrubbing, gloves, gown and sheet are advised. Practically, however, this advice does not seem to be followed. The majority scrub, and those who are frank enough to say they do not scrub do wear gloves. It is to be noted that of the sixteen who do not wear gloves, eight agree that infection can be carried into the pleura; and of seventeen who do not wear a gown, nine agree; and of the five who do not use sterile sheets, three also agree as to infection. The only two who deny exogenous infection, use unusual technique, one changing gloves between each patient and the other stating that the operator does not touch the instru-

ments. No opponent of skin cleansing was found. Although the majority of clinicians do not use sterile gloves or gown, it is not recommended that this procedure be adopted, particularly by beginners, since it is felt that exogenous infection does occur and unfiltered air from a machine has been shown to yield streptococci. It is gratifying to note that only five men do not use a cotton filter.

The Olive View Clinic uses the wet technique, but for no particular reason except that that is the method which was first instituted here. In the survey it is noted that the authors use the dry method, but that only six of the clinicians use it, and the ten others who answer favor the wet needle. Among the arguments advanced for the use of dry technique are, first, that the wet method is much more painful than infiltrating with a fine needle of 23-g. or more; and, second, that any moisture in the lumen of the pneumothorax needle lessens its calibre and to some extent interferes with free manometric oscillations. These arguments are advanced by Howson (13) and other Southern California clinicians who use this method. It would be interesting for other clinics to adopt the dry method and report on it.

As to anaesthesia, the stated opinion in the literature and practice is given emphatically for its use, although two state it is not used on refills. There is a belief among some men that the anaesthetic solution on the pleura is the cause of effusions, but opposed to this is the practice of Fischel (14) of using the solution to separate the layers of pleura and his statement that the incidence of effusions is not great. Some older writers were in favor of preoperative morphine or bromides, but the necessity of any drug prior to operation is rare at this institution.

The type of needle opens up a wide field for controversy. There are five men in the literature and seven in the clinics who use some special form of trocar or pneumothorax needle. Only one man as yet advises an iridectomy knife and with it uses a gauge-18 needle. Of the clinicians, twelve use gauge-18 and four use a gauge-19, from one and a half to two inches long and with general agreement as to blunt point on initial cases. It is gratifying to see this swing away from the trocar or special needle; our experience does not indicate any necessity for their use; indeed, it is felt that the listed dangers of artificial pneumothorax, such as pleural shock, air embolism, or punctured artery or lung, are more apt to occur with the trocar or special needles. Moreover, failure to find the pleural space and to obtain fairly good manometric readings are of rare occurrence at Olive View and this in spite of the fact that most of the work has been done with a gauge-21 needle.

Riviere (5) and Sewall stress the importance of correct readings in pneumothorax and Cutler (9) states that the manometer must guide the amount of air instilled. Hamman and Sloan's (3) summary of the information to be gleaned from the manometer fluctuation is so excellent that liberty is taken to include it here. They state:

1. It indicates accurately when the needle has entered a free pleural space.
2. If the needle is in the lung and the patient holds a deep breath, the manometer records a sudden negative pressure and then falls to normal, but if the needle is in the pleural space, the negative pressure is maintained when the patient holds a deep breath.
3. It indicates roughly the size of the pleural space.
4. If the needle is extrapleural, no true respiratory fluctuations occur.
5. The fluctuation indicates the absorbing power and accurately controls the frequency and amount of refill.
6. The manometer shows a slow increase in pressure with wide respiratory variations to indicate a flexible mediastinum, and a rapid increase in pressure with small respiratory variations shows a rigid mediastinum.

If the manometer gives such information and since Howson (6) very plainly showed the difference in manometer readings with different manometric bores and calibrations, and Proctor (12) of Olive View has secured similar results, it is surprising that more attention has not been given to standardization of this part of the apparatus.

There is a tendency to 4-mm. size tubing, but eleven men use 3-, 5-, or 6-mm. size, and it is felt that tubing and manometer bore should be brought more in agreement. What does it mean for the textbooks to advise using "any standard apparatus," when it is found that only seven men use 4-mm. bore and thirteen men use 5-mm. to 6-mm. manometer bore, and when it is recalled that Howson's (6) 6-mm. bore averaged 3.5-cm. fluctuation and the 4-mm. bore averaged 7-cm. fluctuation? Calibrations of half centimetres and read as centimetres, has been advised as giving the true reading. Perhaps the questionnaire was not quite clear on this, but it seems that only four men use the one-half-centimetre calibration and eighteen use the one-centimetre type.

Along with most clinicians, it is admitted that each case is individual, and that type of disease and amount of collapse, and the securing of a negative sputum and cavity closure are the governing factors. So it was with some hesitancy that questions on amount of air, frequency of refills, and type of pressure were included. The trends are interesting

but there is no thought of standardizing these procedures. The writers and clinicians seem to feel that 150 cc. to 400 cc. is the safe amount to give at first and slightly favor every-other-day refills until the desired collapse is obtained. This is quite a change from the procedure of Murphy (1) who believed in only one injection of air and that of Brauer who gave 500 to 1000 cc. But it must be borne in mind that at that time no one thought of taking chest pictures to determine treatment. In the survey, refills averaged 500 cc. with ranges of from 200 to 1000 cc., the latter amount being given for haemorrhage or in large chests with marked absorption. Weekly refills seem to be favored according to the survey, and this institution uses weekly, bimonthly, and some monthly refills.

Cutler (9) advises always stopping with a slightly negative pressure, and Kramer (7) states that, if positive pressures are necessary for pneumothorax, the case is unsuitable; and Aycock (10) that unpleasant results are due to positive pressures. Since seventeen men indicate they use negative pressures, one might infer that partial collapse is the rule, but this is not entirely the case since four of the men use complete collapse. Riviere's (5) objections to selective collapse are that "all cases do not have a free pleura and that selectives require so much attention that the number of cases one can handle is limited." Aycock (10) makes a rather strong case against complete collapse, maintaining that it causes too much displacement of the mediastinum, compresses comparatively healthy lung, gives more frequent pleural exudates, and the large refills at long intervals disturb the intrathoracic equilibrium. It is felt the best results at Olive View have been obtained with partial collapse and the survey indicates the men as almost equally divided between partial, 13 men, and complete collapse, 11 men. These are interesting points but any further discussion is beyond the scope of this paper.

Fluoroscopy is advised by the literature and the clinicians who answer this query practically all indicate that this check-up is used, and Cutler (15) in the May, 1933, AMERICAN REVIEW OF TUBERCULOSIS emphasizes the importance of routine fluoroscopy in successful pneumothorax work. It is used routinely here, and it is our opinion that only the best trained chest workers should ever give pneumothorax without fluoroscopic information.

Some workers are of the opinion that artificial pneumothorax should be maintained for long periods of time, Dumarest (16) even claiming that a successful pneumothorax should be continued indefinitely. Packard (2) of Saranac Lake holds that an effective pneumothorax of two years'

duration and a negative sputum, "gives reasonable assurance that the lung may be expanded with safety." It is noteworthy that the average time given in the survey is two and a half years.

SUMMARY

In a questionnaire survey of pneumothorax procedures, among 7 authoritative writers and 30 widely separated clinics, which are handling upward of 2,000 cases, there are a number of interesting results.

There seems to be general agreement that infection can be carried into the pleural space by this operation but more than half the men do not use gloves or sterile gown.

The majority of clinicians use the wet technique but rather potent arguments are advanced in favor of the dry procedure.

There is a definite swing away from the use of trocars and special needles to the use of ordinary aspirating needles, about gauge-18 and 2 inches long.

There is much lack of agreement regarding tubing-bore, manometric bore and manometric calibration, and there exists the necessity for standardization of this part of the apparatus.

There is fairly general agreement as to initial amount of air, the use of negative pressures, fluoroscopy, and the length of time the collapse is maintained. The men seem about evenly divided as to the use of partial or complete collapse.

CONCLUSION

It is evident from this survey that some clinics might well check on their records to determine if there is any incidence of skin infections and empyema when sterile procedure is not used throughout. The question of anaesthetic solution as the cause of effusions should be investigated, and information is desired as to the use of calcium salts and fluid restrictions to lessen such effusions. In view of the authors and clinicians who support dry technique, it might be well for some clinics, including our own, to give this method a careful trial. Since it seems fairly evident that manometric bore and calibration differ in various clinics, some authoritative organization should designate a standard apparatus and outline a fairly standardized method of procedure after a study and survey of all types.

Finally, nothing in this paper is to be construed as meaning that anyone ever anywhere can standardize either the patient or his disease.

Acknowledgment is made to those clinicians who kindly answered the questionnaire, and to Drs. Bogen, Seymour and Oechsli for suggestions, particularly to Dr. Proctor in preparing the questionnaire and demonstration.

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DISCUSSION

By Dr. Howson: For many years it has seemed to me highly desirable to effect more standardization for pneumothorax apparatus and technique. The differences in technique in the hands of experts manifested in the response to this questionnaire are not at all surprising, and are of very little significance in so far as getting results with the individual patient is concerned. Standardization here is of particular value to the beginner.

Standardization in apparatus is needed because of the fact that many of these patients travel from place to place during the time they are under treatment, and it is greatly to be desired that the men in the different localities should speak the same language, so that the intrapleural pressure may not be subject to undue variations.

For refills a 20-gauge needle is quite satisfactory in those cases which have free manometric fluctuations, but for the not inconsiderable minority in whom the pressures fluctuate within very narrow limits the 17-gauge needle seems to me to possess definite advantages. I can see no objection to the standard sharp bevel of these needles.

For initial refillings a 21-gauge short-bevel needle is the instrument of choice when the pleural space is free, but, when adhesions are present and one has to make pleural space, I have not found the fine needle so satisfactory, and feel a sense of security with the blunt, fine catheter (about 17 gauge), with the eye on the side.

Admitting the difficulties inherent in selective collapse, it has seemed to me that the least collapse which will effect the desired result is to be aimed at, as the danger of permanent crippling of the relatively unaffected portion of the lung is greatly lessened if it can be permitted a reasonable amount of function.

OLEOTHORAX

With a Report of Cases[1, 2]

CHARLES K. McCARTHY

By the term *oleothorax* is meant the placing of an antiseptic oil in the pleural space. The purpose of this procedure is either to compress the lung or, in cases of empyema, to "antisepticize" the pleural cavity.

Since Forlanini instituted the modern method of artificial pneumothorax, phthisiologists have worked tirelessly to obtain satisfactory collapse of the lung; but, unfortunately, we frequently see cases in which this method is not indicated or is impossible, even though intrapleural pneumolysis has added tremendously to our procedures.

For oleothorax we are indebted to Bernou, who in 1922 first used an antiseptic oil for therapeutic purposes in the pleural space for the treatment of bronchopleural fistulae. Since Bernou, most of the work, as reported, has been done by the French. Comparatively few reports have come from this country, the most notable being the well-known clinical study by Ray Matson.

There is considerable difference of opinion among workers in tuberculosis as to the efficacy of oleothorax. The selection of the case, the absolute care in technique, and a rigid observation of the patient are essential features in the use of this valuable procedure

Indications: To-day we consider six conditions in which oleothorax is indicated:

1: Disinfection oleothorax: In which effusion is removed and replaced with oil.
2: Inhibition oleothorax (oleothorax antisymphysaire): In which the oil is used to prevent reëxpansion of the lung when sufficient collapse is impossible in the face of an imminent obliterative pneumothorax.
3: Compression oleothorax: To obtain the degree of collapse desired when this is impossible with air alone.
4: To close cavities held open by adhesions when intrapleural pneumolysis is impossible.

[1] From the Rutland State Sanatorium, Rutland, Massachusetts.
[2] Read before the Worcester Section of the Massachusetts Medical Society at the Rutland State Sanatorium, October 11, 1933.

5: To promote rigidity of the mediastinum; for a movable mediastinum will offer no resistance to the pressure of the lung and satisfactory collapse is impossible.
6: In cases of pleuropulmonary fistulae with small openings.

Contraindications:

1: In Europe it is sometimes used in cases of artificial pneumothorax when it is difficult for the patient to obtain frequent refills of air. This, I believe, should never be done. These patients require constant observation and much stricter discipline than an ordinary case of artificial pneumothorax.
2: It is contraindicated in bronchopleural fistulae of large dimensions.
3: Pleural effusion of serous character occurring in the course of artificial-pneumothorax therapy.
4: As a means of maintaining collapse in cases in which air is rapidly absorbed. In these the oil may act as an irritant and defeat the desired end by causing an obliterating pneumothorax. More frequent refills are more efficient and safer in maintaining the desired collapse.

Oil: We have used gomenol in olive oil. Gomenol is a volatile oil obtained by distillation of the leaves of *melaleuca viridiflora*, a plant indigent in Northern Africa. Considerable work has been done in an effort to establish definitely its bactericidal properties.

Clerc showed that gomenol inhibited the growth of human tubercle bacilli on gelatine cultures, and also that animals inoculated with tubercle bacilli to which gomenol has been added lived much longer than did the controls.

Some workers substitute paraffin oil in cases in which the pleura is found sensitive to olive oil.

Technique: The apparatus used here is the ordinary pneumothorax needle and a water manometer. We use the two-needle method: that is, one needle is connected to the syringe by a rubber tube, and the other needle to the water manometer. By this means, both needles are inserted into the pleural space, and, as the operator injects the oil, he can gauge the pressure by the manometer readings.

Testing the sensitiveness of the pleura: Here we use a test-dose of 5 or 10 cc. of oil. This may be followed by a febrile reaction for a day or so which, in the usual case, rarely exceeds 100°. If this rapidly declines,

it is fairly safe to proceed. A few days later, a larger dose may be given, say 25 cc., and this is increased every few days until the desired quantity is instilled.

Frequent fluoroscopic examinations are made in order to check carefully on the results obtained and also the appearance of an exudate which, on account of the greater density, will underlie the oil.

In our cases, we have followed Matson's technique and have kept the intrapleural pressure neutral or slightly negative.

After the oil has been instilled, the patient is required to lie on the opposite side after the oil has been massaged from the needle tract, to prevent sinus formation.

Oil replacement: We find that the oil is absorbable in varying amounts. Evidently there is a difference in the absorption rate in different patients. Usually, however, we find that replacement of a small amount, perhaps 25–50 cc., is necessary in anywhere from a month to three or four months; this, of course, in compression cases. If we are dealing with a pyopneumothorax, we replace the oil at weekly intervals after washing the pleural space with normal saline or boric-acid solution.

Complications: We have been fortunate in our cases in the matter of complications. We have had no cases of air embolus or perforation of the visceral pleura. We believe this to be due to the fact that we have kept the manometric pressure strictly neutral or negative. It is high pressure which probably causes these complications.

Although most of the cases in this series are comparatively new, none have, as yet, developed a purulent exudate. Serous-exudate formation has taken place in several with no serious results.

Results

This series consists of 14 cases of pulmonary tuberculosis treated during the past four years at Rutland State Sanatorium.

The oleothorax was performed for the following indications:

	cases
1. Disinfection oleothorax	5
2: To close bronchopleural fistulae	2
3: Compression oleothorax to close cavities	4
4: Inhibition oleothorax—obliterative pneumothorax	3

Of the disinfection cases, one (practically a terminal case) died in six weeks. The other four are living and are improved—one slightly and the other three markedly so.

Of the cases of bronchopleural fistulae, one is dead (this was considered a terminal case on admission). The other is slightly improved, with the fistula apparently closed.

Of the compression oleothorax cases, all four are improved: one has had thoracoplasty; one has been discharged from the hospital; and the other 2 are markedly improved. Sputum is negative.

Of the inhibition oleothorax cases, one was discharged home, with sputum negative, and collapse reëstablished; one is doing well, with sputum negative, is gaining weight, is ambulatory, and collapse is re-established; the third is doing well, has no sputum, is ambulatory, and collapse is reëstablished.

CONCLUSIONS

1. Oleothorax has proved in this series of cases to be an effective method in combating progressive pulmonary tuberculosis after other methods have failed.
2. It is effective in the face of an obliterative pneumothorax.
3. It will sometimes collapse cavities which have resisted all other methods.
4. It is helpful in cases of pyopneumothorax.
5. It is not dangerous to the patient if carefully performed.
6. I believe that the procedure merits more extensive study and trial.

I wish to express my appreciation to Dr. Ernest B. Emerson and the other members of the medical staff for their coöperation in preparing this report. I also express my appreciation to Mr. D. Robinson, a working patient, who prepared the photographs of the X-ray films.

Figs. 1 to 4: Case M. M.

FIG. 1. Admission plate. Artificial pneumothorax begun. Two large cavities shown.

FIG. 2. Cavities still present, held open by adhesion.

FIG. 3. Following intrapleural pneumolysis. Beginning obliteration in right base. Small amount of oil and small effusion.

FIG. 4. Oleothorax established with complete closure of cavities.

Figs. 5 to 8: Case M. C.

FIG. 5. Admission plate. Marked involvement of left upper lobe.

FIG. 6. Pneumothorax established. Excellent collapse of pathological portion.

FIG. 7. Lung reëxpanding. Obliterative pneumothorax.

FIG. 8. Oleothorax established. Collapse reëstablished.

FIG. 1

FIG. 2

FIG. 3

FIG. 4

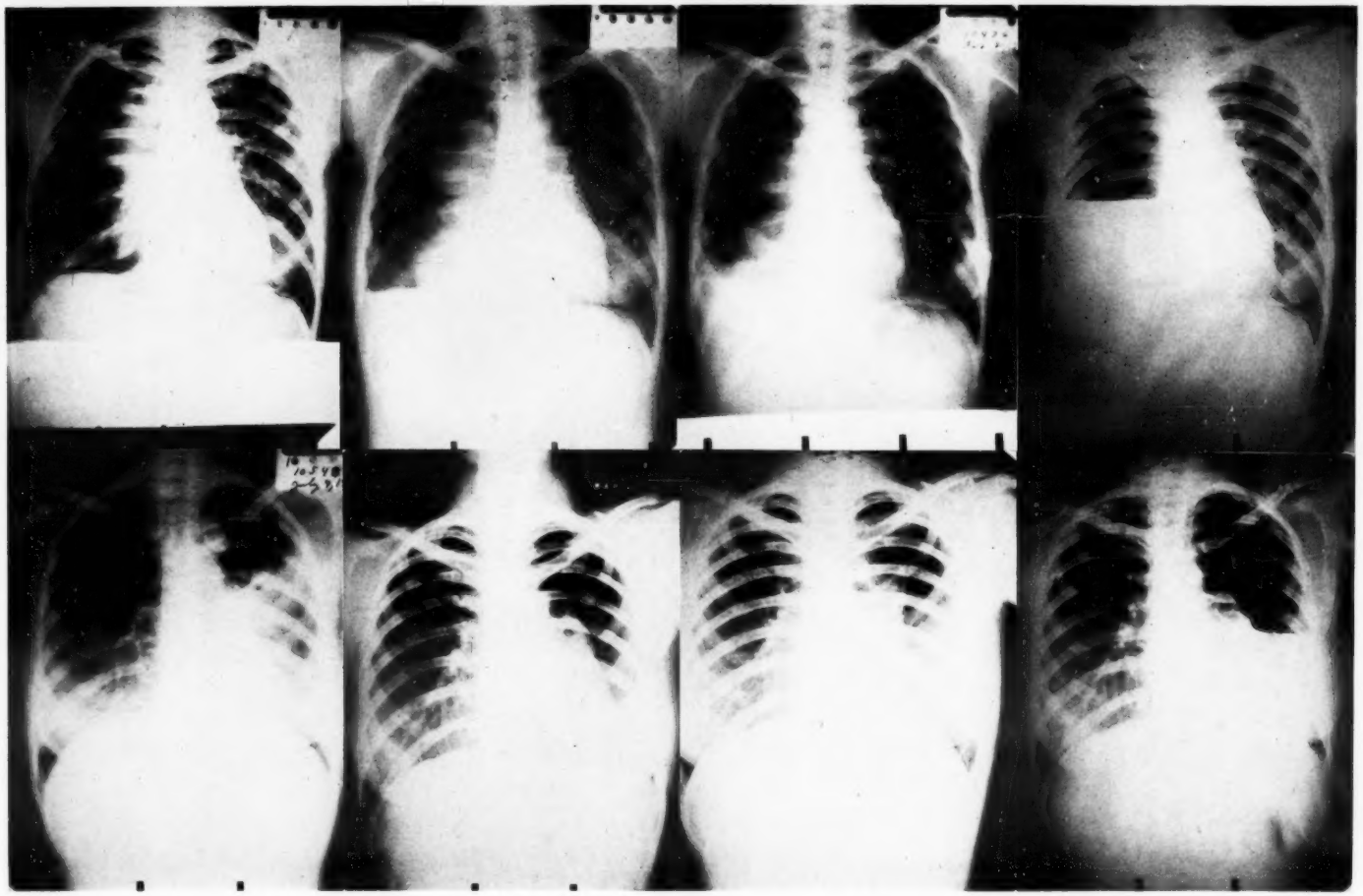

FIG. 5

FIG. 6

FIG. 7

FIG. 8

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THE PATHOGENICITY OF *MYCOBACTERIUM TUBERCULOSIS* (*AVIUM*) FOR DOGS BY INTRACEREBRAL INJECTION[1]

PAUL E. STEINER[2]

The use of virulence tests in different species of animals, which is the accepted method for determining the type of an unknown strain of *Mycobacterium tuberculosis*, is not entirely satisfactory when it involves the use of chickens because of the frequency of spontaneous tuberculosis in this animal. A similar objection applies to the use of chickens for isolating avian tubercle bacilli from suspected materials. The possibility of a preëxisting tuberculous infection is not entirely eliminated by testing the chickens with tuberculin and using only those which are not tuberculin-sensitive.

The results of Feldman's experiments (1) (2), with intracerebral injections of avian tubercle bacilli in dogs, suggest the possibility of using the dog as a more reliable test animal for isolating and testing the virulence of strains of the avian bacillus. Spontaneous tuberculosis of the central nervous system in this animal has not been reported, so that with a reasonable degree of certainty we may conclude that in injected animals, dead with tuberculosis, the material introduced was the source of the infection. Feldman found that while intraperitoneal, intrabronchial or enteric inoculations were never fatal and massive intravenous doses produced death in only a few cases, intracerebral injections of avian bacilli were invariably fatal. The infecting doses that he used were rather large, whereas the materials that we wished to test contained the microörganisms only in small quantities if at all. It therefore seemed advisable to determine the effects of the intracerebral injection of known amounts of avian tubercle bacilli, weighing them as accurately as possible, and using rather small doses. The possibility of considerable variation in the virulence of cultures of different strains of avian origin was also considered worthy of investigation. Finally, the effects of the injection of tissues infected with the same strains of bacilli were studied.

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[2] Fellow in Medicine, National Research Council.

EXPERIMENTAL PROCEDURE

Twelve miscellaneous stock dogs of both sexes and various ages, under the usual laboratory care for a week or more before use, were injected intracerebrally in the left frontal region under ether anaesthesia with sterile surgical precautions. The injections were made in the earlier experiments through a small trephine opening. Later it was found that the skull could be easily perforated with little trauma and no haemorrhage by a small nail after preliminary incision of the skin. The injection was made slowly through this opening with a small needle. The perforation was made just behind the ridge palpable on the skull outlining the upper limit of the frontal sinus. This avoided injury to the motor cortex. The animals appeared normal as soon as the effects of the anaesthetic were gone, no pareses or paralyses being noticed.

Three different strains of *Mycobacterium tuberculosis*, considered to be avian types, were used for the injections. The first strain used was obtained from Dr. Florence B. Seibert and is the avian strain (designated hereafter as the "NTA" strain) being used by the various groups in the extensive chemical investigations by the National Tuberculosis Association. Its history is well known. The second strain used (designated hereafter as "P1" strain) was isolated in 1931 from a tuberculous chicken by Dr. Truman Potter of this university (Chicago). It is virulent for pigeons and for rabbits. In the latter, intravenous injections of 0.5 to 1.0 mgm. cause death in about one month. The third strain (hereafter designated as "C18" strain) was isolated by the writer from a tuberculous chicken in 1932. It readily produced fatal tuberculosis in other chickens. Its virulence for rabbits by the intravenous route was not tested, but injected intraperitoneally it produced an extensive tuberculosis fatal in six weeks.

Injections of these three strains were made, using doses varying from 0.1 to 1.0 mgm. moist weight of the bacilli per kilogram dog body-weight. The ages of the culture were from 25 to 44 days. Those cultures that reached their maximum growth on their particular medium soonest were allowed the shortest growth-periods. They were grown on the solid medium to which they were accustomed and on which their virulence had previously been tested. The "NTA" strain was grown on Long's synthetic and also an egg-yolk medium. The "P1" strain had always been grown on glycerine-agar, and the "C18" strain had always been on the egg-yolk medium. The organisms were suspended in sterile salt

solution, the volume of which was such that the calculated dose for the animal was contained in one cubic centimetre or less.

The dogs were observed daily. Their weights were taken at frequent intervals. Tuberculin tests were made on those that survived for three weeks or more. Both human and avian O.T. and in some instances the highly purified tuberculin proteins prepared by Seibert (3) were used for intracutaneous tests. One-tenth cubic centimetre of concentrations up to 50 per cent O.T. was used with never a definitely positive skin reaction, although the animals at autopsy were shown to have a tuberculous infection.

At autopsy the animals were carefully examined for evidence of a tuberculous infection. The brains were hardened in formalin, and tissues from the injection site in the left frontal region, the right occipital lobe and the medulla were studied microscopically. Tissues from the other organs were fixed, usually in Müller-formol solution, embedded in paraffin, and the stained sections studied. Haematoxyln and eosin and the Cooper modification (4) of the Ziehl-Neelsen stain were used routinely on the sections and other stains for special studies as indicated. The animals that did not succumb to the infection were autopsied at intervals after sixty days, one animal being allowed to survive for one hundred and seventy-five days. In a few experiments inoculations of material from the meninges were made on appropiate media at autopsy.

Results

A study of table 1 shows that the extent and severity of the disease produced by the above procedure vary more with the virulence of the strain used than with the dosage. This is evident from the duration of the period of survival, but more convincing evidence is to be had from a study of the histopathology. The "NTA" strain of bacilli was least virulent, causing death in three animals on the 17th, 41st and 65th days, but permitting survival in good health in three other dogs until autopsied on the 60th, 60th and 175th days. With the other two strains of organisms fatal infections were produced in every instance, death occurring between the 6th and 31st days. This comparison of duration of survival is not entirely just, because with the "P1" and "C18" strains larger doses were given to most of the dogs. However, in two animals in which the smallest dose of 0.1 mgm. per kilo was given, the duration of survival and the pathological picture produced corresponded to that

of the other experiments with these strains and not to that produced by the less virulent "NTA" strain.

The disease produced in the infected dogs resembled that described by Feldman. Soon after the injection the dogs appeared normal in every respect. They ate well, gained weight and played or fought

TABLE 1

ANIMAL NUMBER	STRAIN OF BACILLI	AGE OF CULTURE IN DAYS	DOSE PER KILO	SURVIVAL IN DAYS	CENTRAL NERVOUS SYSTEM			TUBERCULOSIS ELSEWHERE		
					Gross	Histological	Bacilli	Gross	Histological	Bacilli
			mgm.							
2	"NTA"	44	0.1	41	Abscess	Meningitis; abscess	+ +	0	Liver?	
3	"NTA"	44	0.1	60*	0	Abscess	++	0	0	
4	"NTA"	44	0.1	60*	Abscess	Meningitis; abscess	+++	0	Liver?	
5	"NTA"	44	0.1	17	0	Meningitis; abscess	+++	0	0	
11	"NTA"	35	0.1	175*	Internal hydrocephalus	Ependymitis	+	0	0	
12	"NTA"	35	0.1	65	Abscess; adherent dura	Meningitis; abscess	+++	Adhesive pleuritis?	0	
13	"C18"	25	0.5	6	Meningitis	Meningitis	+++	0	Liver	+
14	"C18"	25	0.5	31	Meningitis	Meningitis	+++	0	Liver Spleen	+ +
17	"P1"	28	1.0	11	Meningitis; encephalitis	Meningitis; encephalitis	+++	0	Liver Spleen	+ +
18	"P1"	28	1.0	24	Meningitis	Meningitis; abscess	+++	0	Liver	+
19	"P1"	28	0.1	24	Meningitis	Meningitis; abscess	++	0	Liver	
20	"P1"	28	0.1	24	Meningitis; abscess	Meningitis; abscess	++	0		

* Killed to close experiment.

according to their dispositions. The skin incision healed by primary union, although in a few cases a small subcutaneous granuloma with a slight seropurulent discharge developed. As stated before, several of the dogs remained well. One animal (No. 13) made a sudden exitus on the 6th day three hours after it had been observed to appear normal.

Autopsy revealed an extensive meningitis, and from this exudate pure cultures of acid-fast bacilli resembling the tubercle bacillus were recovered. In contrast to this abrupt course the onset of illness was usually insidious, with slight lethargy, which gradually increased and was followed by tremors and muscular twitching. The animals sought the dark. Their appetite failed; they lost weight and after a few days or weeks coma, spastic paralyses, and sometimes tonic and clonic convulsions appeared.

At autopsy the essential gross findings were confined to the cranial cavity. The skull perforation usually failed to heal with bone, a granulation tissue sometimes extending out under the skin occupying the defect. The dura was usually unduly adherent to the calvarium. In only one case did it appear to be tenser than normal. In some instances there were adhesions between the dura and piaärachnoid, in the older experiments sometimes so dense that they could not be broken.

The changes in the piaärachnoid varied with the strains of organisms used. None of the six dogs injected with the "NTA" strain showed any macroscopic meningitis other than that immediately around the perforation. With the other two strains an extensive meningitis was found, most pronounced over the left frontal and parietal regions but also visible at the base and over the right hemisphere. In some instances there was an asymmetry of the hemispheres caused by a localized bulging of the left frontal cortex. On section of the hardened brains this was seen to be due to abscess formation at the injection site (see figure 1). These lesions consisted of a localized area of softening, surrounded by a thin, firm, brownish wall and, in the larger lesions, a centre filled with a clear jelly-like substance which was coagulated by alcohol but not by formalin. The largest of these abscesses occurred in an animal (no. 20), injected with the "P1" strain, which died twenty-four days after injection. A pure culture of acid-fast bacilli was grown from this brain. This lesion measured 2.2 by 1.8 by 1.4 cm. Some brains revealed no gross change at the site of injection. In certain of these animals a minute lesion was found microscopically and in others none at all.

The lateral ventricles, especially the left, showed a massive exudate in some animals. Dog no. 11, injected with the more benign "NTA" strain, and surviving for 175 days in apparently excellent health, revealed at autopsy a moderate internal hydrocephalus for which there was no explanation grossly. Microscopically there was an extensive sub-

ependymal infiltration by mononuclear cells in which acid-fast bacilli were demonstrable. The swelling and exudate were sufficient, so that the cerebral aqueduct might have been blocked.

Gross pathological changes elsewhere in the body were not significant. A few of the animals had a terminal pneumonia and one of these had a unilateral fibrinous pleuritis. There were no gross lesions suggesting tuberculosis in the lungs, liver, spleen, kidneys or adrenals.

The histopathological pictures produced by these three strains of microörganisms differed even more then the gross lesions, so that they can best be described in two groups. The "P1" and "C18" strains produced similar changes and will be described together.

The meninges in the "NTA" strain dogs showed a slight cellular infiltration by large mononuclears, some plasma cells and a few small lymphocytes. This reaction was not marked and in some instances was limited to the left frontal region. Even here it was somewhat focal. The meninges in some sections showed only a slight diffuse fibrous thickening. The brain substance immediately under the pia mater was not appreciably involved. Lesions were seen at the injection site in five of the six dogs (figure 1). These were of macroscopic dimensions in only three cases. They consisted of sharply circumscribed accumulations of large mononuclear cells among which were numerous plasma cells and some lymphocytes. In the younger lesions the margins showed recent and older haemorrhage. In several of the older, larger lesions there was a heavy fibrous wall, which had, however, been broken through in numerous places, so that here there were smaller mononuclears and lymphocytes in dense foci. The centres of these lesions showed necrotic changes, this material being homogeneous, glassy and eosinophilic. Immediately surrounding such necrotic areas were a few polymorphonuclear leucocytes and also very large mononuclear phagocytes containing fat, blood pigment, and acid-fast bacilli. The capillaries around these abscesses showed a proliferation and considerable infiltration with large mononuclears and a few lymphocytes. Blood-vessels elsewhere in the brain showed slight to no infiltration. In the lateral ventricles and floor of the fourth ventricle, as it appeared in the medullary sections, the ependyma was irregularly involved. The cells were sometimes cuboidal and between and under them were a few large mononuclears. Dog no. 11 which showed the internal hydrocephalus had an extensive ependymitis in all sections.

Stains for acid-fast organisms showed the bacilli to be most numerous

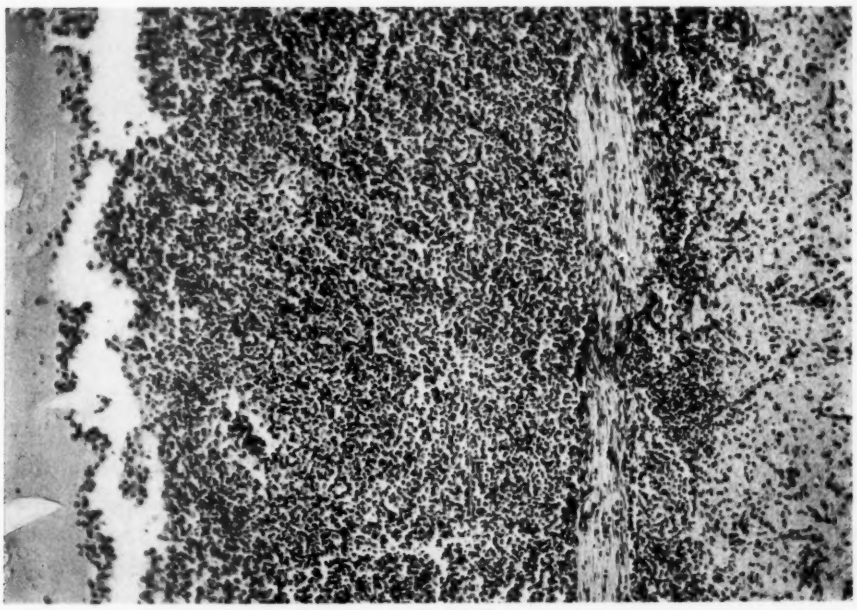

FIG. 1

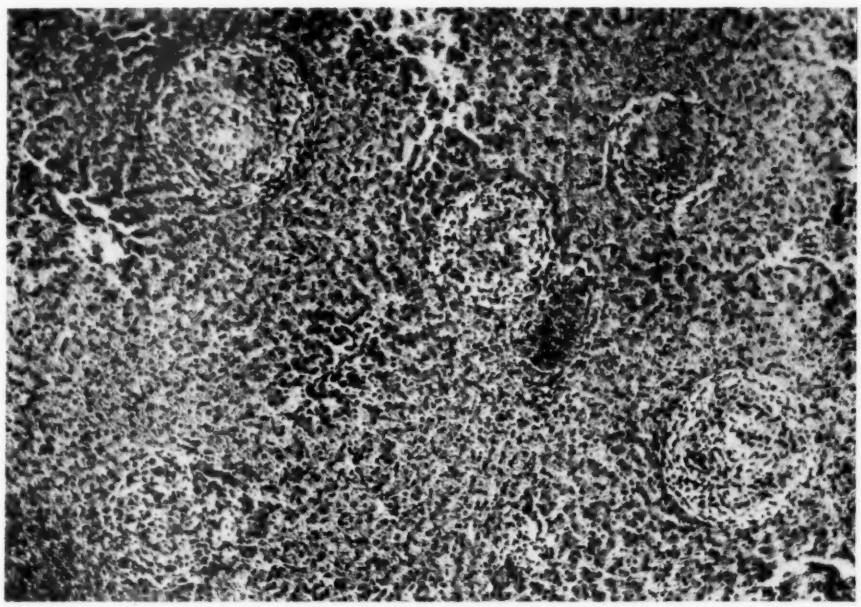

FIG. 2

FIG. 1. Low-power (100) view of a tuberculous cerebral "abscess" showing from the left: central necrosis, wide wall of mononuclear phagocytes, fibrous reaction, invasion through this fibrosis, and the slight diffuse involvement of the brain substance. Dog no. 4, autopsied 60 days after injection with 0.1 mgm. per kilo of the "NTA" strain. Acid-fast bacilli were numerous in this lesion.

FIG. 2. Liver lesions of dog 14, injected thirty-one days previously with 0.5 mgm. per kilo of the "C18" strain. Note the discreteness and absence of surrounding reaction. Acid-fast bacilli were easily demonstrated.

in the large phagocytes near the necrotic centres of the abscesses. These cells often contained the bacilli in such numbers that they could be seen with the low-power objective of the microscope. Out in the new parts of the lesion they were rare. In the meningeal and ependymal infiltrations they could usually be demonstrated without difficulty.

With this strain in no instance were there lesions in lungs, liver, spleen, adrenals, kidneys or lymph nodes definitely shown to be tuberculous. In three of these six animals the liver showed a few, small, irregular foci of mononuclears. They were poorly demarcated from liver cells and were not encapsulated. There was no cellular reaction around them. In no instance could acid-fast bacilli be demonstrated in these lesions.

In the groups of animals inoculated with the "P1" and "C18" strains of bacilli, tuberculous lesions were found in the central nervous system, liver and spleen. Here a much more extensive meningoencephalitis occurred. The meningeal infiltrations were much more marked. In one case there was abscess formation in the meninges. Although the predominating cell was still the large mononuclear, in the dogs that died on the sixth and eleventh days there were many polymorphonuclear neutrophilic leucocytes in the exudate. This meningeal reaction was seen in every part of the central nervous system examined. Under the meninges the cortex was extensively invaded by similar cells, and around the blood-vessels there was a similar reaction. The lesions produced at the site of injection were larger and more diffuse. The fibrous reaction was usually moderate. Necrosis was sometimes present. In the abscesses, also, in the more acute cases polymorphonuclear neutrophiles were numerous. The ependymal reaction in these dogs was more extensive. The blood-vessels throughout the frontal lobe and sometimes much further away showed a marked involvement. Acid-fast bacilli were more numerous and more widespread in meninges and abscesses. They could also be seen in the brain substance below the meninges, under the ependyma, and out from the injection-site abscesses.

These two strains of bacilli produced definite tuberculous lesions in the liver in four of the six animals (see figure 2). These consisted of focal accumulations of medium and large mononuclears sharply set off from the liver cells. Here too there was no cellular or fibrous reaction around the lesions. The liver lesions of the dog that survived only six days showed considerable numbers of polymorphonuclear neutrophiles. In these lesions acid-fast bacilli were fairly numerous. The remaining dogs of this series showed indefinite lesions in which no organisms were demonstrable.

Two dogs of this series also showed lesions in the spleen in which acid-fast bacilli were seen. These were small, round accumulations of mononuclear cells located usually near the outer part of the lymphoid ring of lymphoid follicles. Their cytoplasm was slightly eosinophilic. There was no cellular reaction around them.

In the kidney, atrophic glomeruli were seen. The probable age of these lesions permitted us to interpret them as not related to the present experiments. Here also were found small focal accumulations of lymphocytes in the cortex. They did not appear inflammatory in nature. both types of kidney lesions were seen in control dogs. Acid-fast bacilli were not demonstrated in them.

The lungs in several instances showed pneumonia. No acid-fast bacilli were demonstrable and the changes were considered nontuberculous. The adrenals, jejunum, ileum, caecum and lymph nodes from the thorax and abdomen in the cases examined showed no tuberculosis.

The failure to regularly produce a progressive tuberculosis with these three pure cultures was disappointing. Additional experiments were then done to determine whether the injection of tuberculous-tissue suspensions containing these same strains of bacilli would regularly kill animals.

Chickens were killed by infecting them with injections of the "NTA" and the "C18" strains. One chicken died forty-nine days after infection with the "NTA" strain. There was a generalized tuberculosis. Tubercles were very numerous in the liver and spleen and acid-fast bacilli were present in large numbers. A suspension was prepared by grinding 0.75 gm. each of liver and spleen in 5.0 cc. of physiological saline solution. One cubic centimetre of this was then injected intracerebrally into each of two dogs. Both dogs were apparently in excellent health when overanaesthetized at sixty-one and seventy-one days. One dog on thorough study revealed only a small chronic tuberculous abscess at the site of injection, with a slight subacute meningitis. No tuberculosis was seen elsewhere in the body. The other dog after thorough study revealed only a small amount of subependymal round-cell infiltration in the left lateral ventricle. This was probably tuberculous. No tuberculosis was seen elsewhere.

Another chicken died two and one-half months after injection with the "C18" strain, with a generalized tuberculosis. Liver and spleen tissues containing many acid-fast bacilli were used for preparation of a tissue suspension similar to the above. One-cubic-centimetre amounts of this were then injected intracerebrally into each of two dogs. These

animals remained well until they were autopsied on the sixty-third day after injection. One showed no evidence of tuberculosis anywhere. There was only a slight chronic leptomeningitis which was possibly tuberculous. The other showed a small tuberculous abscess at the injection site and a subacute infection of the piaärachnoid. There was no tuberculosis elsewhere.

Comment

The experiments indicate that intracerebral inoculation in dogs as a method for isolating avian tubercle bacilli would not be dependable. With doses of 0.1 mgm. per kilo death did not invariably result. The amounts employed were not great when one remembers that we were trying to infect an animal of low susceptibility with an organism that usually produces a low-grade, chronic infection. The dosage seems great, however, by comparison with the small number of bacilli that would be injected if one were testing suspected materials, for example, a suspension of ground tissues, since the total volume which can be injected intracerebrally is limited. By the injection into four dogs of tissue suspensions known to contain many acid-fast bacilli slight infections were produced which were not fatal during periods from sixty-one to seventy-one days. Histologically the lesions produced by both strains of organisms used were not progressive.

The type and distribution of lesions produced by the injection of pure cultures varied with the virulence of the organism. The milder reactions were such that they were recognized as tuberculous with considerable difficulty. The usual picture of tuberculosis with definite tubercle-formation, giant cells and caseation type of necrosis was not seen in these experiments.

The difference in virulence of the strains of organisms used was striking. Death occurred earlier and more regularly with those strains that were capable of setting up a severe and widespread meningitis. The less virulent strain in some cases produced rather large lesions in which the organisms were very numerous at the site of injection, but they seemed incapable of spreading. These local abscesses did not seem in themselves to kill the host. By the procedure used in inoculating these animals it was impossible to avoid infecting the meninges by the penetrating needle or to prevent a backflow of inoculum to the meninges after the needle was withdrawn. Nevertheless, the meningitis produced by this strain (NTA) was slight. With the other two more highly

pathogenic strains the lesions were less localized, possibly because of the shorter duration of life and the greater invasiveness of the organisms. Death in these animals seemed to occur from the meningitis before cortical lesions localized.

Although the distribution and the extent of the changes produced by the various strains differed, the essential cellular reaction in experiments of analogous ages was the same. In the early reactions studied the polymorphonuclear leucocytes were an important constituent, at least numerically. They were seen only in small numbers in the reactions at three weeks of age or older, and then mostly in relation to areas of degeneration. Typical small lymphocytes were present in all of the brain lesions, and they were sometimes rather abundant. Their distribution was both focal and diffuse. Plasma cells were sometimes present.

The most prevalent reacting cell was that here called the mononuclear, which has elsewhere been given numerous other names. In these experiments this cell has been extremely variable in size, structure and staining reactions. To us it was morphologically similar in any given animal, whether found in the meninges, localized cortical abscesses, perivascular spaces of the central nervous system or in the liver. It differed somewhat in the various animals according to the duration of the experiment. In size it varied from a cell slightly larger than a lymphocyte to a cell several times as large. In the smaller cells the nucleus was small and had a dense, compact, abundant chromatin content. The cytoplasm was moderately abundant and stained uniformly. These smaller cells rarely contained acid-fast bacilli. Between such cells and the large macrophage with pale nucleus and abundant, vacuolated cytoplasm there were numerous representatives of all stages. They gave the impression of being closely related cells.

Objection might be made to the use of the term "abscess" in referring to the injection-site lesions. When well developed they resembled abscesses. They had a soft, necrotic centre around which there was a cellular reaction forming a definite wall. In the zone near the necrotic centre polymorphonuclear leucocytes were often seen, scattered among the large mononuclears, plasma cells and lymphocytes. There was usually a definite attempt at encapsulation and in the more recent granulation-tissue reaction the proliferation of capillaries was quite evident. The presence of red blood corpuscles and blood pigment in the centres of some of the younger lesions was attributed to trauma at the time of injection.

The failure of these dogs to become sensitized to tuberculin is a confirmation of the findings of numerous other workers with tuberculosis in this animal. We have no explanation for this phenomenon.

SUMMARY

The intracerebral injection of small doses (0.1 mgm. per kilo) of *Mycobacterium tuberculosis* (*avium*) in dogs was not invariably fatal. The pathogenicity of three strains used in these experiments differed greatly. With one strain the lesions were more benign and were confined to the brain and meninges. They consisted principally of abscesses formed at the site of injection and a subacute or chronic meningitis. With the other two strains a more widespread meningoencephalitis occurred with definite lesions in the liver and occasional lesions in the spleen. Death seemed to be due mostly to the meningitis. Life was compatible with large cerebral abscesses containing large numbers of bacilli.

The intracerebral injection of tuberculous-tissue suspensions infected with two of these same strains of tubercle bacilli produced even less extensive infections and no deaths during periods up to seventy-one days. The number of organisms injected by this method was probably less than when pure cultures were used.

The polymorphonuclear leucocyte was present in abundance in the early lesions of the central nervous system and liver. The essential reacting cell was the mononuclear phagocyte. Small lymphocytes and plasma cells were present in variable numbers. Giant cells were not seen in any of the lesions.

The results indicate that this procedure would not be dependable as a method for detecting *Mycobacterium tuberculosis* (*avium*) in suspected materials.

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THE CULTIVATION OF THE TUBERCLE BACILLUS FROM THE BLOOD-STREAM BY LOEWENSTEIN'S METHOD[1]

EUGENE MAIER

The circulation of tubercle bacilli in the blood-stream has been affirmed for a long time by many investigators. Enough circumstantial evidence has been accumulated to the effect that at one moment or another tubercle bacilli must be present in the blood-stream of many patients suffering from tuberculosis and tuberculous infection. The efforts of students in this field have been concentrated on methods by means of which direct proof of the circulating bacillus in the blood-stream could be furnished. A short discussion will be given of the methods employed by various workers, in historical order, beginning with an era when the aetiology of the disease was still unknown.

1: 1868–1903: Inoculation and direct smear (Ziehl)
2: 1903: Jousset's method
3: 1910: Stäubli-Schnitter method; acetic acid and antiformin
4: 1910–1912: Period of recognition of errors: Brem, Beitzke, Schern and Dold.
5: 1905, 1909, 1914, 1919, 1930: Attempts at cultivation from the circulating blood—Loewenstein, Anderson, Faber, Clough.

1: 1868–1903: As the early workers in this field were fairly sure that the causative agent of tuberculosis must be present in the blood, they resorted to animal experimentation, which in their time was best suited to solve the problem. Villemin (1), in 1868, was the first successfully to transmit the disease from a case of miliary tuberculosis to a rabbit. Weichselbaum, Garvey, Bergeron and others followed with similar reports. During this time direct smears of the blood stained by the method of Ziehl were prepared by certain workers. However, this method, because of shortcomings too obvious to mention, failed to solve the problem.

2: Jousset's method—1903: Jousset's (2) idea was to destroy the blood cells by digestion with pepsin and make the bacillus more easily visible

[1] From the Pathological Department of Bellevue Hospital, New York City.

for identification by the direct smear after staining. The positive results obtained with this method were so high as to arouse considerable doubt when presented to the scientific world.

3: Stäubli-Schnitter acetic-acid and antiformin method: In 1910 Stäubli (3) introduced 37 per cent acetic acid for haemolysis of blood and the subsequent preparation of smears stained by the method of Ziehl. Schnitter (4) supplemented this technique by employing Uhlenhuth's antiformin to further concentrate the blood after haemolysis.

4: 1910–1912. Period of recognition of errors: Brem (5), Beitzke (7), Schern (6) and Dold: The methods of Jousset and Stäubli-Schnitter led numerous investigators astray in that positive findings of tubercle bacilli in the circulating blood were so general as to arouse grave doubt. Even in the blood of normal persons (Kurashige (12)) acid-fast bacilli were found. Brem, in this country, was the first to call the attention of workers in this field to the fact that distilled water, used in the Stäubli-Schnitter method, may contain acid-fast bacilli. Acid-fast bacilli were found in faucets and in rubber hose connected with bottles containing distilled water. Beitzke, Schern, Dold and Kahn substantiated Brem's claims, which also held true of Jousset's method, since distilled water was employed in this procedure, together with pepsin, which was found to contain acid-fast bacilli regularly. Even in antiformin acid-fast bacilli were found. It is obvious that Brem's contributions discredited the positive results obtained by numerous investigators and justified existing doubts.

5: Attempts at cultivation: With the possibility of such errors in mind, a group of workers turned to cultivation and to animal experiments. In 1905 Loewenstein (8) reported successful cultures on potato-glycerine-agar from the blood of experimentally infected animals. In 1909 Anderson (9) reported the successful transmission of tuberculosis by the transfer of infective blood through a number of generations. Furthermore, he successfully cultivated the blood of infected rabbits. Faber (10), in 1914, with blood from a child dead of miliary tuberculosis, grew the bacillus on blood-agar. In 1919 Clough (11) reported cultures from the blood taken during life from patients with miliary tuberculosis. In a review of 1297 cases collected from the literature, which were acceptable to this author as to their reliability, 6.7 per cent of guinea-pig inoculations with blood gave positive results.

In recent years Loewenstein has given a new impetus to this problem by reporting succesful cultivation of the tubercle bacillus from the circu-

lating blood. Sumiyoshi (13), working in his laboratory, described a new method for the isolation of tubercle bacilli from infected material. They found that tubercle bacilli resist the action of sulphuric acid while the accompanying bacteria are killed. The material is mixed with a 15 per cent concentration of sulphuric acid, repeatedly shaken and kept in contact for ten to fifteen minutes, including centrifugating at high speed.

Loewenstein and his disciples applied the sulphuric-acid method in combination with the cultivation of the tubercle bacillus from the bloodstream. The medium which he recommends resulted from his researches on the chemical nature of tuberculin free from albumin. In this medium asparagin forms the source of nitrogen superior to peptone, which is usually the basis of nitrogen in other media. Loewenstein is convinced that peptone damages the development of the tubercle bacillus on the medium. The synthetic part of his medium is given as follows:

Potassium phosphate, primary	1 gm.	Asparagin	3 gm.
Sodium citrate	1 gm.	Glycerine	60 gm.
Magnesium sulphate	1 gm.	Distilled water	1000 cc.

To 150 cc. of this solution, 6 gm. of potato flour and 12 gm. of glycerine are added, which gives a 14 per cent concentration of the glycerine. The solution is boiled for fifteen minutes and kept at 56°C. until dextrine is formed. To 150 cc. of this mixture, four eggs and the yolk of one additional egg are added, plus 5 cc. of a 2 per cent Congo-red or malachite-green solution. After filtration through sterile gauze, 5–6 cc. are poured into test-tubes. The tubes are slanted and inspissated for two hours at 80° to 85°C. on two consecutive days. For control of sterility, the tubes are incubated over night at 37°C.

For the taking of blood the automatic ampule of Kovacs, containing 3 cc. of 10 per cent sodium citrate, is recommended by Loewenstein. Ten cc. of blood are taken, which does not coagulate for at least two weeks. Shipments of blood in such ampules have been received by Loewenstein from all parts of Europe, some being on their way more than eight days.

In the laboratory the contents of the ampules are transferred to wide heavy-walled test-tubes. Centrifugation is done at high speed and, after pouring off the serum, 3 per cent acetic acid is added. Haemolysis will occur after repeated shaking. After prolonged centrifugation at high speed, the acetic acid is discarded; the sediment is washed with sterile distilled water and decanted. If the sediment has lost its red color and

has taken on a gray color, a second washing is not necessary. The haemoglobin is removed by this process, as it is detrimental to the development of the tubercle bacilli because of its oxygen-binding capacity. The sediment is now ready for distribution over the surface of the medium by capillary pipettes in amounts of 0.5 to 1 cc. Four tubes are thought sufficient for each case by Loewenstein. The tubes are sealed with sealing-wax, and stored horizontally in the incubator at 37°C., in order to prevent the material from collecting at the bottom of the tubes.

If there is any doubt as to the sterility of the blood, a second series is recommended by treating the rest of the sediment with 15 per cent sulphuric acid for ten minutes. Centrifugation and washing, as described above, are necessary.

The first control of the cultures is done macroscopically after twenty days, microscopically after five weeks. In many cases small colonies have been observed after two weeks; after four weeks numerous colonies may be seen, as, for instance, in cases of polyarthritis acuta, in which, literally, one colony arises from every drop of blood. The macroscopic aspect of the colonies varies considerably. A large number of strains cultivated from the human blood grows greasy, as the bacillus of chicken tuberculosis. The greater number of strains grows dry, wart-like, forming sometimes a continuous dry film.

Loewenstein in a table presents the following results:

	Number of Cases	*Positive*
Lung	140	54
Skin	92	51
Larynx	28	18
Kidney	22	13
Bones	18	9
Eyes	4	3
Rheumatismus acutus	21	21

Russew (14), working in Loewenstein's laboratory, haemolyzes the blood by the addition of distilled water, which, in our and other workers' experience, gives less bulk in the sediment. Otherwise, his technique is identical with Loewenstein's. Of 17 cases of pulmonary tuberculosis, 6 were positive; of 8 cases of surgical tuberculosis, 6 were positive.

Schwabacher (15), in a report of 11 cases, had one positive culture in a case of bronchitis and pleurisy with effusion. The sputum was negative; blood culture in broth-trypsin was negative; the blood, spinal fluid, urine and sputum were examined cytologically and by culture, with

negative results. Blood cultures on Loewenstein's egg medium, somewhat modified by replacing starch with 5 per cent glycerine-broth, gave a growth of tubercle bacilli in 16 days.

Jontofsohn (16), in an attempt to repeat Loewenstein's work, reports the result on 40 cases of pulmonary tuberculosis, in 3 of which an invisible growth was noticed. He used Loewenstein's original method as well as Russew's modification. He is unable to say why his positive results are so few in comparison with those of Loewenstein and his disciples, the more so since he followed Loewenstein's technique in every detail. In controls he cultivated the blood of 6 tuberculous guinea pigs and one tuberculous rabbit, obtaining positive cultures in two specimens from the guinea pigs.

Machioro (17) examined the blood from 118 tuberculous patients on Hohn's medium. As he does not give any figures, we assume that his results were negative. However, he concludes that tubercle bacilli circulate at one time or another in the blood-stream, a theory which is based on pathological findings. The sojourn of the bacilli is of short duration, which makes proof of their presence in the blood-stream extremely difficult.

Bingold (18), in 1928, reported 326 cases of tuberculosis of all stages in which blood cultures were done systematically on different media. In only one case did the culture become positive by using the Eppendorfer tubercle-bacillus beaker for the isolation of the bacillus. In a later series of 43 cases, this investigator obtained three positive cultures.

Hohn (19) was the first to indicate the possibilities of the sulphuric-acid method for extensive use in the laboratory, mainly for the pure culture of the tubercle bacillus from infected pathological material.

Schattner (20), in a critical study, compares the effects of sodium hydroxide and sulphuric acid in various concentrations and concludes that sulphuric acid is better able to kill off the contaminations than sodium hydroxide. At the same time he finds that tubercle bacilli grow more quickly in the culture after treatment with sodium hydroxide than after contact with sulphuric acid.

Author's Experiments

Loewenstein's favorable results caused us to undertake the cultivation of a large number of blood specimens from patients in the tuberculosis wards of Bellevue Hospital. Altogether, 198 cases of pulmonary tuberculosis in advanced II and III stages were examined, all with positive

sputa. The composition of Loewenstein's medium varies considerably as the comparison of his formulae shows. We started our work in April, 1931, at a time when Loewenstein's later formula was not known to us.

	1930 Formula	*1931 Formula*
Potassium phosphate	400 mgm.	100 mgm.
Magnesium sulphate	40 mgm.	100 mgm.
Sodium citrate	100 mgm.	100 mgm.
Asparagin	600 mgm.	300 mgm.
Glycerine	2 gm.	6 gm.

The greatest discrepancies are contained in the later formula as far as the concentration of glycerine is concerned, since one is in doubt whether or not a 6 per cent or a 14 per cent concentration is intended by Loewenstein. As a 14 per cent concentration is rather high, we decided to adhere to this high concentration; later on we varied the concentration of glycerine, using 8, 10 and 12 per cent concentration in various supplies of media. The results on sputum controls were practically the same, no matter what concentration was used, the period of contact with the acid and the virulence of the organisms having more influence on the growth of colonies. A positive sputum of a high Gaffky scale may give not more or fewer colonies than a sputum of low Gaffky scale, assuming that each bacillus is capable of producing a colony. This phenomenon leaves no doubt that in a sputum of high Gaffky scale a great number of bacilli are no longer capable of reproduction, be it that their virulence is lowered or that the effect of the contact with the sulphuric acid reduces their vitality to nil.

We used for the greater part of our work tubes of 14- and 28-mm. diameter, together with petri dishes of usual size (7.5 cm.). After inoculation, the plug was pushed into the tube for about 1 cm. below the edge, the proximal end of the plug clipped off, and the tube sealed with hot paraffin. The petri dishes, after inoculation, were left in the incubator for 24–48 hours until the surface of the medium appeared dry. A strip of adhesive tape, 2.5 cm. in width, was placed around the circumference of the dish, cut and lapped over the bottom. The plates were then kept up-side-down in the incubator.

As the medium was mixed with a 2 per cent Congo-red solution with a pH range of 3–5, being red on the alkaline side, no information concerning the hydrogen-ion concentration could be derived from it. The greatest care was taken in surveying the pH of the medium before and after the addition of the eggs. The final pH was always fixed from 6.5

to 7.2. The quality of the medium was furthermore controlled by the cultivation of strains of H37, *BCG* and their pure cultivation in sputum. Incubation was carried out at a temperature varying from 36.5° to 38.5°C.

Another test serving as a control was made as follows: Fifty cc. of blood were withdrawn from a rabbit's heart and to this a suspension of a virulent human strain was added. Contact of the suspension with the blood was allowed to go on for two hours at incubator temperature. After this the specimen was treated according to Loewenstein's methods and the sediment inoculated in a number of tubes. A growth was visible in the tubes with a magnifying glass after six to eight days.

Macroscopic controls of the tubes and plates inoculated with human material were made at frequent intervals from ten to twelve days. After six weeks the tubes and plates were opened and examined microscopically by making a Ziehl-Neelsen smear. The surface of the medium was wiped off with a sterile cotton swab on a wooden stick. One smear was made of each tube or plate, a careful search of which failed to disclose acid-fast bacilli or visible colonies on the medium in a single case. The period of our investigation was from April 14 to July 1, 1931.

DISCUSSION

The results of other workers obtained by different methods vary considerably. There is little doubt that the attempts to demonstrate bacilli in the blood-stream microscopically by smears stained by various methods cannot be regarded as convincing proof, and have little more than historical interest. And yet the direct microscopic method was used only recently by Sato and his associates, together with the guinea-pig inoculation method. It seems that he does not regard the direct method very highly. He prefers and recommends as the method of choice the inoculation of guinea pigs, supplemented by a pathological-anatomical study to prove the presence of bacilli in the blood-stream. The injection of guinea pigs with blood from tuberculosis patients has to be considered as the method known to give the most exact results so far. Differences in the results obtained by various workers are not quite as divergent, but they are in no way uniform. There are different sources of possible error which may account for the discrepancies in this method. The method of injection and the amount of material injected, the number of bacilli contained in the injected material and their virulence, the period of observation, the proportion of protecting substances injected together with the blood, may decide positive or negative results.

There is no doubt that a culture method as proposed by Loewenstein should prove itself superior to the guinea-pig test, if for no other reason than that it would shorten the time required for a test. There is one case in our records in which the injection into a guinea pig of spinal fluid from a case of tuberculous meningitis did not give positive results, while the same spinal fluid plated on Loewenstein's media gave a number of colonies. Superiority of the culture method has been proved in many more cases by Hohn and Von Eiselsberg. In no laboratory should difficulties be encountered in the preparation of a sediment from the blood-stream suitable for inoculation on solid media. The differing results in control work obtained by Loewenstein's method may be attributed to differences in the preparation of the medium. Busson (21) proposes that, in order to get results comparable with Loewenstein's, the institutions in greater Vienna should employ media from Loewenstein's laboratory. He is convinced that such a procedure might clear up the differences in the results which have persisted so far.

Concerning the preparation of the medium, Loewenstein does not mention to what pH the medium should be standardized. It is known that the pH range for the growth varies considerably, depending on the strain. As Loewenstein has said, there are many more strains which can be cultivated from the blood-stream than the accepted number of two or three, and it is fair to assume that the pH for their optimum growth may not be the same in every case. On the other hand, tubercle bacilli coming from the blood-stream are adapted to the pH of the body fluids and the continuance of this pH on the artificial medium should give a certain guarantee for successful cultivation. Nevertheless, the transfer of tubercle bacilli from the blood to an artificial medium means undoubtedly a thorough change of environment with consequences to its vitality beyond our control. Sharp (22) found the normal figure for the pH of fresh eggs at 7.6. As stored eggs lose carbon dioxide, a shift to the pH from 7.6 to 9.7 occurs. Busson demonstrates one case in which joint-fluid planted on a medium containing Congo-red gave a growth five times better than on a malachite-green medium. Loewenstein does not discriminate between the two dyes. In our own experience, working on tuberculous sputa, the use of malachite-green was given up in favor of Congo-red. In comparing cultures from the same specimen of sputum, there was no doubt that Congo-red gave a richer growth. Hohn prefers eggs with dark yolks to those with light yolks. To what extent the results of the Loewenstein method could be varied by any one of the

foregoing points, cannot be said. However, it is difficult to explain entirely negative results in a large number of cases on the assumption that variations in technique resulting from shortcomings in the description of Loewenstein's method are responsible.

Loewenstein's latest work was extended to infections of the skin in which a tuberculous aetiology was suspected. In cases of lupus vulgaris, lupus erythematodes, erythema induratum, granuloma annulare, polyarthritis acuta, lupoid, ulcus tuberculosis miliare and others, his blood cultures were positive in a greater proportion of cases in early spring and decreased toward the summer and fall. From this Loewenstein concludes that the conditions for the improvement of a patient are more favorable in summer when the bacilli tend to disappear from the blood-stream, and that the circulation of bacilli is indicative of an active process in the body. Calmette, as a result of numerous experiments, was led to believe that the above group of diseases is caused by a filterable virus or filterable form of the tubercle bacillus. Fischer is convinced that this is not the case and that these diseases are now definitely recognized as bacillaemias by the Loewenstein method.

Liebermeister's (23) latest statement, in the *Deutsche Tuberkulosetagung* (1930), is to the effect that the only reliable method of proving the presence of tubercle bacilli in the blood-stream of human beings is the guinea-pig inoculation test.

SUMMARY

In 198 cases of advanced pulmonary tuberculosis, attempts to cultivate the bacillus from the blood-stream by the Loewenstein method gave negative results.

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SUPPLEMENT TO
THE AMERICAN REVIEW OF TUBERCULOSIS

Editor: ALLEN K. KRAUSE, Tucson, Arizona

Vol. XXX DECEMBER, 1934 No. 6

PURIFIED PROTEIN DERIVATIVE

A Standardized Tuberculin
for
Uniformity in Diagnosis and Epidemiology

By

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JOHN REICHEL, L. T. CLARK AND
ESMOND R. LONG

With an Introduction by
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Published Monthly at Mount Royal and Guilford Avenues, Baltimore, Md.
By the
NATIONAL TUBERCULOSIS ASSOCIATION
Business Office, 50 West 50th Street, New York City

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INTRODUCTION

WM. CHARLES WHITE[1]

Progress in chemistry has made it clear that it should be as readily possible to separate from the tubercle bacillus, or the medium on which it is grown, the pure fraction responsible for the skin reaction in tuberculous individuals as it is to separate adrenalin or cortin from the adrenal gland or insulin from the islands of Langerhans in the pancreas.

This, therefore, early became one of the major problems of the Committee on Medical Research of the National Tuberculosis Association.

While Old Tuberculin, as prepared by Robert Koch, was one of the first biological agents used for diagnosis and therapy, and the best Old Tuberculins are very stable, probably due to the high percentage of glycerol contained in them, and very potent in eliciting the skin reaction, still, as pointed out by the British and American commissions, there has been a vast variation in those offered for use. This has been the case not only in those prepared by manufacturing houses, but in those produced by Health Departments of municipalities, states and governments.

These variations were in the content of skin-reacting substance, ranging from almost none to very powerful concentrations. They occur as a result, first, of using different culture media for the bacilli, with resultant great variation in specific protein production and retention of foreign or nonspecific protein substances, and, second, of using strains of tubercle bacilli of different nature. Often as many as three to four strains of different character were used in the preparation of one lot of tuberculin (as for example human, bovine and avian strains).

A clinician thus was never sure that the results with one tuberculin were comparable with those obtained from the use of a second supply of tuberculin, nor comparable with those of another clinician who might be using a tuberculin of entirely different strength and character. As a matter of fact the results were not comparable. Therefore many of the stories in the epidemiology of tuberculosis from a national or international viewpoint were greatly reduced in value.

[1] Chairman of the Committee on Medical Research of the National Tuberculosis Association.

To this variation in strength of tuberculin was added difference in methods of dilution and of individual technique. Dilution has always heretofore been on a fluid basis with respect to a supposed known content of the original fluid Old Tuberculin. This, as is well known, can never be as accurate as one based on the weight of pure substance in a constant quantity of the same diluent.

In addition to all of these difficulties there have been many different tests proposed from time to time (for instance, the Pirquet, the Calmette, the Moro, the subcutaneous and the intracutaneous tests). Much time has been spent, one might say wasted, over a discussion of these. We know now that the upper layer of the living skin is the site of election for eliciting the test reaction. Therefore, most careful instruction must be followed by the individual clinician in introducing a measured quantity of the reaction substance in the most uniform way to obtain comparable results.

The above paragraphs will indicate the problems which the Committee has had before it. The first step in their answer was to provide a common constant medium on which to grow the bacilli, a medium free from foreign protein, and one in which the bacilli would produce in sufficient quantity the protein substance desired, and by preference a medium free from color. This was provided by Dr. Esmond R. Long after years of experience and experiment. In the general studies on the chemistry of the tubercle bacillus carried out under sponsorship of the Committee on Medical Research, the Mulford Laboratories of Sharp and Dohme, through Dr. John Reichel, provided pure chemicals in one purchase for this medium to last in constant character over a period of ten years of study. This formed a base-line not only for the protein isolation studies but also for the further work of comparative study on the biological chemistry of different strains of tubercle bacilli.

During the first year or two of work it was found that the substance desired was present both in the bacillus and in the medium after the bacilli had grown to a sufficient culture bulk. The isolation of the substance from the medium was soon found, from a practical and commercial standpoint, to be the method of election. From the initiation of the whole investigation the Committee has had the good fortune to have the keen interest and practical work of Dr. Long and Dr. Florence Seibert, who for years had had the problem before them as one of great importance, were skilled in the chemical and biological methods required for its solution, and had paved the way by fundamental studies on the metabolism of the tubercle bacillus.

It was soon found that the protein fraction sought was probably produced by all strains of tubercle bacilli, but in different quantity by different strains, and further that the specific fraction was a part of a large molecular complex, which might be disintegrated to a certain degree with retention of those specific qualities responsible for the diagnostic skin reaction. The separation of this smaller fraction from the larger molecule requires careful and nondestructive chemical technique, and, while the study is still in progress, the results are such as to justify the present step in the direction of uniformity of method of clinical application.

During the progress of the work the Committee was so fortunate as to bring its studies into coördination with those of Dr. Marion Dorset of the Bureau of Animal Industry. For many years under Dr. Dorset's direction there has been produced a stable Old Tuberculin in quantity almost the equal of the combined production of the rest of the world. This has been used as the basis of diagnosis of tuberculosis in cattle. The fact that reacting cattle have been killed and subjected to postmortem study makes of the Bureau's campaign the greatest epidemiological study of tuberculosis in the world. Dr. Dorset was one of the first to show that the Koch method of standardizing Old Tuberculin by the guinea-pig-killing test might be erroneous, for he and his associates have been able to separate the guinea-pig-killing fraction from the skin-reacting fraction. He was also early in seeing the need for discarding protein-containing media, and in providing a synthetic medium for producing the requisite substance. In the past year Dr. Dorset has replaced Old Tuberculin in routine work in the study of tuberculosis in cattle with the new synthetic-medium tuberculin.

The coördination of the studies of tuberculosis in man and cattle should lead us far in our knowledge of the epidemiology of this disease. There are, however, important differences in the study of the disease in the two species. Man has a thin and clear skin, and the forearm is the site of test injection. In cattle the thicker caudal fold is used. Human beings infected with tuberculosis are, as a rule, far more sensitive to tuberculin than infected cattle, and respond to a much lower dose. In cattle a positive reaction signs the death-warrant of the reactor. In man positive reaction gives no license for slaughter. On the contrary the test may be repeated many times in the same patient for its prognostic significance. Moreover, as succeeding papers in this series will show, not only the incidence of infection but also the intensity of response to

tuberculin have epidemiological importance. Therefore the need for a substance of great refinement, accurate for diagnostic, prognostic and possibly therapeutic use in man, is an imperative one.

With the knowledge that it had gained over the production of the skin reactive protein substance by the bacilli, in the desire for uniformity of its production and method of use, the Committee next adopted the medium of growth, the strains of bacilli and the technique in preparation of tuberculin, in use in the Bureau of Animal Industry as worked out and perfected by Dr. Dorset for the cattle studies. This was fortunately a comparatively simple step, as the medium prepared by Dr. Dorset differs from that devised by Dr. Long mainly in the addition of glucose and the use of a larger quantity of asparagine, which give a greater yield in bacilli and production of the desired protein molecule. Dr. Dorset uses three strains of tubercle bacilli, which Dr. Seibert has found to yield practically equal amounts of protein. The use of the same medium for tuberculin production established, then, a sound base-line for both human and cattle studies, and allowed at the same time a path for isolation of the pure substance desired for the delicate demands of human work.

The isolation of this pure fraction in the hands of Dr. Seibert has proceeded with rapidity, although the determination of its exact molecular size and structure has not yet been finally accomplished. There has been established, however, the firm foundation for a uniformity of substance which can be quantitatively diluted, for method of preparation and for a technique of administration which will carry far forward our knowledge of the epidemiology of tuberculosis in men and cattle.

The protein fraction now prepared by a uniform method from a uniform medium by the growth thereon of known strains of bacteria, is a constant substance. The method of distributing the minute quantities necessary for individual and group testing has been perfected. A diluent of constant character is provided with each package. Each new batch of tablets, made as described in this series of papers, is carefully tested by Dr. Seibert and Dr. Long, by clinical trial on a sufficiently large series of human beings, and it is believed that tuberculin in this form furnishes a basis not only for more accurate diagnosis but for uniform statistical studies.

There are those, of course, who will be reluctant to give up Old Tuberculin, which in its best form has been such a useful agent, particularly where local statistical studies have long been carried out with the same product. Discrepancies and needed improvements may be found in

the present step, but the Committee is sure that all will agree that, when the day comes that all physicians and epidemiologists use the same pure substance in the same way, our knowledge in the field of epidemiology will rapidly increase.

The Committee on Medical Research, through its Subcommittee on Tuberculin, of which Dr. Long is Chairman, will welcome all suggestions and criticisms, and will endeavor with patience and such skill as it possesses to coördinate and plan its work for the future to accomplish the final purpose of uniformity in this field of great practical importance.

THE ISOLATION AND PROPERTIES OF THE PURIFIED PROTEIN DERIVATIVE OF TUBERCULIN[1,2]

FLORENCE B. SEIBERT

The method which has been chosen as most satisfactory and practical for the isolation of the active principle of tuberculin responsible for the tuberculin skin reaction was first briefly described among other methods, in 1932 (1). The product was then called *SOTT*, meaning "synthetic medium old tuberculin trichloracetic acid precipitated," to fit into a scheme of abbreviated nomenclature. It has since been studied more extensively. The essential steps leading to its preparation are as follows: (1) growth of the bacillus on a synthetic medium; (2) preparation from these cultures of an *SOT* (that is, Old Tuberculin from synthetic medium); (3) concentration and removal of impurities from this *SOT* by ultrafiltration; (4) precipitation of the active principle, that is, the purified protein derivative (or *SOTT*), by trichloracetic acid; and (5) removal of the acid with ether, resulting in a simultaneous dehydration of the protein derivative to powder form. The various steps in the process have been described from time to time, but will be assembled here consecutively as actually carried out in the complete process.

THE SYNTHETIC MEDIUM

The liquid upon which the tubercle bacilli are grown is a nonprotein synthetic medium, containing only simple pure constituents. It is the medium used by the Bureau of Animal Industry in the preparation of their synthetic medium tuberculin, for which the formula follows (2):

l-Asparagine	14.00 gm.
Dipotassium Phosphate C.P. ($K_2HPO_4 \cdot 3H_2O$)	1.80 gm.
Sodium Citrate C.P. ($Na_3C_6H_5O_7 \cdot 5\frac{1}{2}H_2O$)	0.90 gm.
Magnesium Sulphate U. S. P. ($MgSO_4 \cdot 7H_2O$)	1.50 gm.
Ferric Citrate U. S. P. VIII (Scales)	0.30 gm.
Dextrose of the grade known as cerelose	10.00 gm.
Glycerol C.P.	100.00 gm.
Water to make	1,000.00 cc.

The reaction should be pH 7.

[1] Aided by a grant from the Committee on Medical Research of the National Tuberculosis Association.

[2] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

The medium is filtered to a clear solution and sterilized at no higher than 10 to 12 lbs. pressure for no more than twenty-five minutes. It should then not be darker than straw-color, and it usually contains a light flocculent precipitate which disappears as the cultures develop.

This medium differs from Long's synthetic medium (3), which has been used in numerous chemical and biological investigations under the cooperative research plan of the National Tuberculosis Association, in the following important respects. The asparagine content is nearly two and a half times higher than in Long's medium, the glycerol content is twice as high, 10 per cent dextrose is added, and there is no carbonate nor ammonium ion except that which arises from the asparagine. The growth of the human-type tubercle bacillus upon this medium is considerably heavier than on Long's medium, as a result probably of the additional glycerol and asparagine content and the dextrose.

Preparation of a synthetic-medium Old Tuberculin: Three strains of the human-type tubercle bacillus, which have been used for many years by the Bureau of Animal Industry and which were kindly given to us by Dr. Marion Dorset, are grown for six to eight weeks at 38°C. upon the synthetic medium described above, and from these cultures the tuberculin is prepared according to the following method recommended by Dr. Dorset and used by the Bureau of Animal Industry.

Equal quantities of the cultures from the three strains, which have been shown microscopically to be uncontaminated, are mixed and then killed by heating in the Arnold sterilizer for three hours. The cultures are filtered through paper and washed with distilled water. Glycerol is then added to the filtrate in the proportion of 122 cc. to each 1000 cc. of the volume of the original culture fluid, and the mixture is concentrated on a steam-bath to one-fifth of this original volume. To this concentrate an equal volume of one per cent phenol in distilled water is added, which gives a resulting concentration of five-tenths per cent phenol. After standing for a few days in the cold until any precipitate has had time to collect, the product is filtered through the Mandler, Berkefeld or Seitz filters. The finished product is two-fifths of the original volume of culture fluid and contains the equivalent of 25 per cent Old Tuberculin.

Concentration and purification by ultrafiltration: Because of the high content of glycerol it is advantageous to dilute this synthetic-medium

Old Tuberculin before beginning the ultrafiltration. The dilution is made with 0.5 per cent phenol. The ultrafiltration is then carried out, using 13 per cent gun-cotton membranes, which are made as follows: Alundum extraction shells of medium porosity (RA 360), 45 mm. in diameter and 127 mm. in length, or any other size, are impregnated by means of suction during immersion for one minute under a gun-cotton solution made by dissolving 13 gm. of dried gun-cotton,[3] designated as "high temperature nitro-cellulose, 15–30° viscosity" in 100 cc. glacial-acetic acid. After the minute is up, the suction is broken very gently and the excess of gun-cotton solution is allowed to drain while the shell is rotated. As the last drop is draining the shell is rotated momentarily up-side-down to give a smooth, rounded bottom, and then it is gently supported under luke-warm water for at least an hour to permit the membrane to set. After this it is placed in running water over night to remove the excess of acetic acid, and finally distilled water is sucked through until the filtrate gives no test for acid with methyl-red. For further details, the original paper (4) should be consulted.

It has been found that when membranes are made properly in this manner, no bubbles can be seen to extend through the membrane, and when a negative pressure of 25 inches of mercury is applied by suction, 130–190 cc. of water will be pulled through the membrane in one hour.

The quantities of tuberculin to be purified at one time, and the purpose for such purification, will determine whether it would be profitable to use a thinner membrane, such as one of 11 per cent strength, which would permit a faster filtration but some loss of tuberculin.

One shell or a number of such shells attached in series can be used for a filtration, depending upon the quantity of tuberculin to be purified. They are immersed in the tuberculin solution, and when suction is applied to the inside of the shell, the noncolloidal constituents of the tuberculin, water, glycerol, etc., are sucked through, leaving behind the active protein fraction and polysaccharide. The ultrafiltration is continued by adding 0.5 per cent phenol to the solution outside the membrane as the level of liquid lowers, until the filtrate coming through the membrane gives no test for chlorides. It is then reasonably sure that the residue remaining behind on the outside of the membrane is as highly purified as possible at this stage in the process. It is then concentrated to a

[3] Gun-cotton from Charles Cooper & Co., 194 Worth St., New York City, has been found to be satisfactory. Ordinary collodion is not an adequate substitute.

small volume by continued ultrafiltration, and finally passed through the Seitz, Mandler or Berkefeld filter.

Precipitation of the purified protein derivative: After the process just described, the solution consists mainly of protein and protein derivatives and a considerable amount of polysaccharide. For analyses of such fractions, see previous publications (4) (5). The polysaccharide is removed by mixing the solution with one-fourth its volume of a 50 per cent aqueous solution of trichloracetic acid (freshly prepared and filtered), which makes a final concentration of 10 per cent. The resulting precipitate, which consists almost entirely of protein products (1), is thrown down by centrifugation, after standing from four hours to overnight. The supernatant solution is decanted, and can be saved as a convenient and rich source of tuberculin polysaccharide.

The precipitate is repeatedly washed by centrifugating (six to eight times) with fresh 10 per cent trichloracetic acid until the washes are practically colorless. The more thoroughly it is washed at this stage, the lower the content of reducing substances in the final product.

After this final washing the precipitate is smeared in a thin layer inside the tube and partially dried *in vacuo* to remove the excess of water, thus hastening the dehydration. Complete drying should by all means be avoided, since the product becomes dark and horny. From here on all manipulations should be done in a hood and the worker should be protected by cotton in the nostrils or with mask, to guard against inhaling any of the powder which may be scattered by means of the ether vapors. Large volumes of ether are used to extract the trichloracetic acid from the precipitate by means of alternate triturating and centrifugating until the ether gives no acid reaction with litmus. The precipitate, which is now crumbling in the ether, is treated with ether many more times to cause complete dehydration. A light tan-colored powder results. This is the Purified Protein Derivative or *SOTT* (synthetic medium Old Tuberculin trichloracetic acid-precipitated).[4]

For use, this powder may be weighed and dissolved to any strength, even to 10 or more per cent, by suspending in water or saline and adding the smallest amount of tenth-normal sodium hydroxide necessary to give a clear solution. The solution, presumably of the sodium salt of the protein, is brought back to neutrality with tenth-normal hydrochloric acid, and in this form at concentration of 1 per cent or more is stable

[4] The initials P. P. D. are now used as an abbreviation for the manufactured product. See page 766.

indefinitely. For tuberculin testing this solution can be diluted serially, as in the case of Old Tuberculin, or the powder may be incorporated in tablet form, as described in a later paper in this series by Clark.

Chemical nature of the purified protein derivative: This product is soluble, as just stated, on the addition of a small amount of alkali and remains soluble at pH 7.0 or even very slightly on the acid side. It is precipitable with all the reagents which precipitate proteins, such as ammonium sulphate, alcohol, hydrochloric, acetic, trichloracetic and phosphotungstic acids, salts of heavy metals, etc. The color reactions for the different amino acids in proteins are all positive, such as the biuret, vanillin, glyoxylic acid, ninhydrin, Millon's, xanthoproteic and diazo tests. The Molisch reaction is faint. A nitrogen-partition analysis (6) showed percentages of the various nitrogen fractions within the normal range for other proteins, except that the total basic nitrogen fraction was somewhat high. Whether or not this may be due to the presence of a small amount of nucleic acid, as found in more recent studies (7), must be determined by further research. The total nitrogen content is about 14.5 per cent, and the content of reducing substances appears to be from 1 to 6 per cent, according to the method of reduction used in making the measurement.

This Purified Protein Derivative is held back to a very large extent by thick parchment, and almost completely by a 13 per cent gun-cotton-glacial-acetic-acid membrane, as described above. Thinner membranes permit a large percentage of the active material to diffuse, as has been shown by Le Guyon and Weil (8), Maschmann and Küster (9), Kallós and Hoffmann (10), and myself (5).

This behavior of the fraction, together with the facts that it is not coagulable by heat, and is stable in solution, leads one to believe that it must be a relatively small molecule compared with most well-known proteins. As a matter of fact, the molecular weight, determined by the osmotic-pressure method (11), has proved to be approximately 2000 to 4000. A size such as this, in view of the properties described, would serve to classify the molecule among the proteoses or even polypeptides.

Relationship between molecular size, antigenicity and potency of the various tuberculin fractions: In view of the fact, however, that tuberculin protein obtained from unheated tuberculin by precipitation with ammonium sulphate has a molecular weight of about 25,000, and the further fact that this molecule can be split into smaller ones of molecular

weight about 2,000, with practically no loss in weight, nitrogen, or in potency, the following views have appeared tenable (11):

The smallest molecule containing full tuberculin skin potency is a polypeptide of a definite low molecular weight, in the neighborhood of 2,000 or less. If this is true, it should be possible to isolate it as a pure chemical entity, with the view toward determining the special linkage or structure responsible for the activity. Varying numbers of these units may be aggregated to form larger and larger molecules, which would, therefore, have the same nitrogen content and same potency per milligram of nitrogen or weight, as the smallest unit.

According to this view fractions such as the M9 (5) or MA 100 (12), which have been purified from unheated tuberculins by means of ammonium sulphate, and found to have a molecular weight of about 25,000, would represent the larger aggregates. The TPT (1), which was made by trichloracetic-acid precipitation, and has a molecular weight of about 3,000 to 8,000, would also be an aggregate, but intermediate in size. The smallest potent molecule so far isolated, the *OTT* or *SOTT*, products made by trichloracetic-acid precipitation from heated Old Tuberculin and synthetic-medium Old Tuberculin respectively, with molecular weights of about 2,000 or less, would represent the units from which the aggregates are formed. The fact that similar small molecules of this same size can be made by cautious alkaline treatment of the larger molecule (11) supports this view.

It is highly significant that, as the size of the tuberculin protein molecule is decreased, there is an accompanying loss in antigenicity (11) (13), until, in the case of the *SOTT*, practically the entire power is lost for eliciting an Arthus reaction, producing precipitins or of precipitating highly immune serum. Nevertheless, the specific tuberculin potency is unchanged. Intracutaneous injections of 0.000,01–0.000,02 mgm., by weight, cause definite reactions in sensitive persons. Therefore the specific tuberculin potency seems inherent in the smallest unit. Furthermore, it has recently (14) been shown that the *SOTT* can be rendered antigenic by adsorbing it on aluminium hydroxide, thus demonstrating its hapten-like nature.

Yield of purified protein derivative: The protein derivative can be produced with a high degree of uniformity in quantity and in potency, as recorded in table 1, in which figures are given of the yield from various strains of tubercle bacilli grown in two different laboratories.

TABLE 1

STRAIN OF HUMAN-TYPE TUBERCLE BACILLUS USED	SOURCE OF MATERIAL	GRAMS PURIFIED PROTEIN DERIVATIVE OBTAINED PER LITRE ORIGINAL MEDIUM
PN + DT + C	Bureau of Animal Industry	0.60
		0.59
DT + C	Bureau of Animal Industry	0.61
PN	Bureau of Animal Industry	0.63
PN	The Henry Phipps Institute	0.53
C	The Henry Phipps Institute	0.75
DT	The Henry Phipps Institute	0.56
H37	The Henry Phipps Institute	0.21

The study represented by table 1 was made primarily to determine if equal quantities of the Purified Protein Derivative per litre of original medium were produced by the three human strains of tubercle bacilli used in the Bureau of Animal Industry, and also to compare the relative quantity and potency of these preparations with similar preparations made from other strains, such as H37.

The results show the constancy with which the laboratory of the Bureau of Animal Industry has been able to reproduce its new *Synthetic Medium Tuberculin* by carefully ensuring uniformity in all steps in the process of preparation. On the other hand, the liability of different laboratories to vary in attempting to produce a uniform *Synthetic Medium Tuberculin* can also be seen, in the example cited, of varying yield of protein derivative from the "PN" strain in tuberculin produced in the Bureau of Animal Industry laboratory and in our own laboratory. Undoubtedly the variation was due to lack of uniformity in the growth in different flasks in our laboratory. A scant growth in a few flasks or a slightly less growth in many flasks would lower the final yield of potent substance in the pooled mixture. Furthermore, the data show the necessity of a universal use of the same strains, if equally potent unpurified tuberculins are to result. For example, an Old Tuberculin made from an equal number of flasks of H37 culture would have only about one-third the potency of a tuberculin made exactly similarly from the PN, DT or C strains. It is, therefore, easy to understand why the Old Tuberculin preparations on the market vary to such a great extent. As will be pointed out later (15), this variation greatly impairs the value of Old Tuberculin in epidemiological studies in human beings, and also in the individual case, where it is desired to compare skin reactions obtained at one time with those at other periods.

All of these difficulties would be eliminated by the use of a purified powder preparation, such as that described in this paper. The dose used in every case contains a known quantity of the powdered substance, which in turn will check in its potency and chemical composition (nitrogen content, etc.) with another preparation used years previously. Any variation in the luxuriance of growth on various flasks will make no difference in the final product, except that scant growths give a smaller yield of the active fraction. The potency per unit weight of the product obtained from a scant growth is identical with the potency per unit weight of the product from a luxurious growth.

Furthermore, the strain of bacilli used (that is, within the same type) makes no difference in the potency of the final purified product, but merely in the yield of that product. For example, the active substance obtained from the H37 strain, while present in only about one-third the quantity, is nevertheless equal in potency per unit weight to the products obtained from the other human strains, PN, DT and C.

SUMMARY

The active principle of tuberculin has been isolated and purified by means of trichloracetic-acid precipitation from a solution of heated tuberculin prepared on synthetic medium and concentrated and washed by ultrafiltration. The chemical and physical properties indicate that it is a protein derivative with a low molecular weight. It is nonantigenic, in that it does not sensitize or lead to antibody production, but it is as highly potent and specific in the tuberculin skin test as the proteins of larger molecular weight, contained in unheated tuberculin, which are typical antigenic substances.

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THE MANUFACTURE OF THE PURIFIED PROTEIN DERIVATIVE OF TUBERCULIN

JOHN REICHEL[1] (Part I) AND L. T. CLARK[2] (Part II)

PART I

In the manufacture of the Purified Protein Derivative of tuberculin three strains of human type tubercle bacilli, "C," "PN," and "DT," furnished by the Bureau of Animal Industry of the United States Department of Agriculture, are cultured separately on an equal number of flasks containing approximately 100 cc. of Bureau of Animal Industry synthetic medium, the formula of which is:

l-Asparagine	14.00 gm.
Dipotassium Phosphate C.P. ($K_2HPO_4 \cdot 3H_2O$)	1.80 gm.
Sodium Citrate C.P. ($Na_3C_6H_5O_7 \cdot 5\frac{1}{2}H_2O$)	0.90 gm.
Magnesium Sulphate U. S. P. ($MgSO_4 \cdot 7H_2O$)	1.50 gm.
Ferric Citrate U. S. P. VIII (Scales)	0.30 gm.
Dextrose of the grade known as cerelose	10.00 gm.
Glycerol C.P.	100.00 gm.
Water to make	1,000.00 cc.

Reaction pH 7.0.

The medium in the flasks is sterilized by a single exposure to steam under 10 to 12 lbs. pressure for 25 minutes. The tubercle bacilli are grown on the surface for 8 weeks at 37°C. and should average 1.85 gm. of dried organisms per 100 cc. of medium.

PREPARATION OF PURIFIED PROTEIN DERIVATIVE

From cultures on this synthetic medium, tuberculin is made according to the method of the Bureau of Animal Industry (1). The completed product is equivalent to what has been called BAI Tuberculin (Intradermal Special F). The method of production is as follows:

The cultures are killed by means of Arnold steam sterilization for 3 hours and the dead bacilli are removed by straining through gauze. Glycerol is added to the filtrate in the proportion of 122 cc. of glycerol to

[1] From the Mulford Biological Laboratories, Sharp and Dohme, Philadelphia, Pennsylvania.

[2] From the Research and Biological Laboratories, Parke, Davis & Co., Detroit, Michigan.

each 1,000 cc. of the volume of the original culture fluid. The filtrate is then concentrated on a steam bath to one-fifth of the original volume of the culture medium. After this evaporation an equal bulk of 1 per cent phenol in distilled water is added to the cooled tuberculin, reducing the phenol to 0.5 per cent. The tuberculin is allowed to stand for a few days in the cold until any precipitate resulting from the addition of phenol has had time to collect and settle. The tuberculin is then passed through a Mandler filter candle. It contains the equivalent of 25 per cent Old Tuberculin.

It is next subjected to the process of ultrafiltration as described by Seibert (2) in the production of what she formerly designated as *SOTT* (3) (Synthetic Medium Old Tuberculin Trichloracetic acid-precipitated). A battery of glass containers equipped with alundum cups coated with soluble gun-cotton is filled with the liquid tuberculin prepared as described above. Single lots of six litres of tuberculin can be handled most effectively. Filtration is expedited by diluting with an equal volume of 0.5 per cent phenol in distilled water. For this quantity of fluid ten alundum cups are commonly used. A negative pressure of 25–28 inches of mercury is applied to the series of alundum cups, and from 100–1,000 cc. of fluid, depending upon the pressure attainable, and the degree to which filtration has progressed, are pulled through the cups per hour. The liquid remaining behind retains the Purified Protein Derivative. As it filters, the volume is maintained by addition of 0.5 per cent phenolized distilled water, and the ultrafiltration continued until the filtrate is almost chloride-free. The residual fluid is then concentrated to about a quarter of the volume of the original tuberculin by continuation of the ultrafiltration process (the further the concentration the less trichloracetic acid needed to precipitate). It is then passed through a filter candle to remove any insoluble material or foreign particles. It is next mixed with one-quarter of its volume of 50 per cent trichloracetic acid. In the concentration of 10 per cent trichloracetic acid thus produced, the Protein Derivative is thrown down as a tan-colored precipitate. The mixture is allowed to stand over-night and then centrifugated. The supernatant fluid is saved as a byproduct, rich in tubercle-bacillus carbohydrate. The precipitate is washed repeatedly with 10 per cent trichloracetic acid solution until the washes are practically colorless. After the final washing the precipitate is partially dried under vacuum, complete desiccation being avoided, and triturated in anhydrous ether until all the trichloracetic acid and the last trace of

water are removed, leaving a light brown powder, the Purified Protein Derivative of tuberculin. An average of 0.5 to 0.6 gm. per litre of original culture medium is thus secured.

PART II

MANUFACTURE OF STERILE TABLETS OF PURIFIED PROTEIN DERIVATIVE OF TUBERCULIN

A method of incorporating small quantities of highly potent substance with an inert powder in tablet form has previously been described (4). This method has been adopted in the preparation of tablets containing the Purified Protein Derivative.

As described in the accompanying papers by Aronson (5) and Long, Aronson and Seibert (6), doses of 0.000,02 mgm. for the first test and 0.005 mgm. for the second test (reinjection of negatives to the first test) have been found most practical. In order to make these doses available tablets are made containing ten times these amounts. When one of these is dissolved in one cubic centimetre, 0.1 cc. furnishes the required dose.

In the article to which reference has been made (4), *Beta lactose* has been found a suitable solid diluent for a substance to be used in such small quantities as tuberculin protein. It has no deleterious effect whatsoever on the keeping qualities or the solubility of the tuberculin powder, as proved in a series of experiments kindly carried out by Dr. H. S. Willis of the Maybury Sanatorium, Northville, Michigan, and Dr. Barnwell of the Department of Medicine, University of Michigan. In the procedure of manufacture 0.5 gm. of the Purified Protein Derivative is dissolved in a small amount of water with the aid of a little 0.1-normal sodium hydrate and the solution is then neutralized with dilute hydrochloric acid. This is then brought to one litre by the addition of sterile water and adjusted to a pH of 7.0 with the aid of suitable indicators and the potentiometer.

All apparatus and reagents are sterile. The solution remains clear. In it 40 gm. of sterile *Beta lactose* are next dissolved. The resultant solution is evaporated to dryness *in vacuo*, and the dry powder thoroughly ground and thus made ready for further dilution with *Beta lactose*. This is accomplished by mixing the mixture of Protein Derivative and lactose in several stages with small quantities of lactose, with thorough grinding in a sterile mortar at each stage, until the desired proportion of lactose and

Protein Derivative is finally produced. At the end the entire mixture is ground for two hours in a ball mill.

The proportion reached is such that a quarter-grain of the final mixture will contain ten times the required dose. First and second strength powders are prepared, the former containing 0.000,2 mgm. and the latter 0.05 mgm., of the Purified Protein Derivative per quarter-grain of lactose. Ninety per cent alcohol, containing 0.4 per cent tricresol, is used as an excipient and agent to ensure sterility. The uniform powder, moistened with this excipient, is spread on a standard mold, and tablets of quarter-grain weight compressed by hand.

For convenience of administration the tablets are supplied in two types of container, with suitable amounts of sterile diluting fluid in which to dissolve them. The diluting fluid is a buffered saline liquid made from the following solutions:

KH_2PO_4: 9.078 gm. dissolved in 1000 cc. distilled water.
$Na_2HPO_4 \cdot 2H_2O$: 11.876 gm. dissolved in 1000 cc. distilled water.

Two parts of the solution of the potassium salt are mixed with eight of the sodium salt and 0.25 per cent phenol is added.

For small-scale testing single tablets are placed in sterile 1-cc. vials fitted with a thin rubber cap, permitting the introduction of 1 cc. of sterile diluent, which can be removed aseptically with a tuberculin syringe from an accompanying bottle of diluent equipped with a similar rubber cap. Thus a small vial containing ten doses is provided.

Tablets are also supplied for large-scale testing, ten at a time, in sterile rubber-stoppered shell vials accompanied by a 10-cc. rubber-stoppered bottle of sterile diluent. The desired dilution in this case is made by raising the rubber stopper from the vial of sterile diluent, removing the stopper from the shell vial with the tablets, and carefully allowing all of the tablets to slide into the bottle of diluent. Several minutes, with occasional shaking, should be allowed for complete solution. The solution thus prepared contains one hundred doses of first or second strength, according to which type of tablet has been dissolved.

Only freshly prepared solutions should be used, as dilutions of tuberculin, of this high degree, deteriorate in a short time. The solid Purified Protein Derivative, however, has been kept in the laboratory of Dr. Seibert for two years, without chemical or physical change or any detectable loss of strength, and the method here outlined preserves the substance in the same favorable dry state.

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THE PURIFIED PROTEIN DERIVATIVE[1]

With Special Reference to the Technique of Tuberculin Injections and the Grading of Reactions

JOSEPH D. ARONSON

It is at present impossible to make comparative evaluations of the results of various observers on the incidence of tuberculous infection, because of differences in the mode of application, the potency and amount of tuberculin used, and the interpretation of the results.

It is now generally conceded that the frequently used Pirquet method is less delicate than the intracutaneous test. An extended study (1) has brought out the discrepancies in the two tests. It has previously been shown (2) that tuberculin prepared by different laboratories may vary in potency within wide limits, and subsequent studies have confirmed these results. Moreover, the deleterious effect of age upon diluted tuberculin has not been fully appreciated, despite the fact that as far back as 1909 Mantoux (3) noted that its potency decreased upon standing. Okell (4) observed that a 1:1,000 dilution of Old Tuberculin, kept at room temperature, loses 40 per cent of its potency within 10 weeks, and about 60 per cent within 12 months. I have found that a 1:10 dilution of Old Tuberculin, kept at 37°C., loses an appreciable amount of its potency within 7 to 10 days, and that after several months at this temperature but little of its activity remains.

Because of these variable factors, it is clearly desirable that determinations of the incidence of tuberculous infection be carried out with stable tuberculin of reproducible potency, and that the dosage, mode of injection and interpretation be uniform. The Purified Protein Derivative (previously called *SOTT*), prepared by Seibert by growing tubercle bacilli on a synthetic medium of known chemical composition, removing the salts and water by ultrafiltration and precipitating the tuberculoprotein by means of trichloracetic acid, has the advantage over Koch's Old Tuberculin in that it is free of nonspecific proteins and of salts and that its potency is reproducible.

[1] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

In order to ensure uniform results the following procedure is recommended in giving and reading the intracutaneous test with this tuberculin.

TECHNIQUE OF INJECTION

For convenience of testing, the Purified Protein Derivative is put up in tablet form in two types of container, used respectively in small-scale and large-scale testing, as described by Reichel and Clark (5). The small-size vials contain 0.000,2 mgm. of Purified Protein Derivative for the first dose and 0.05 mgm. for the second dose. The stoppers of the bottles containing the diluent and the tablet of Purified Protein Derivative are carefully cleansed with ethyl alcohol, allowed to dry, and 1.0 cc. of the diluent, which consists of a buffered salt solution of pH 7.4, is added to the tablet through the rubber stopper by means of a sterile syringe and needle. The bottle should be shaken for two or three minutes until the tablet is dissolved.

For the first dose the skin over the forearm is washed with ethyl alcohol or acetone and allowed to dry. By means of a sterile 1.0-cc. tuberculin type of syringe and a 26-gauge needle of half-inch length, 0.1 cc. of the diluted protein derivative, containing 0.000,02 mgm., is injected into the skin over the flexor surface of the forearm at a point about 4 to 5 cm. below the bend of the elbow. The bevel of the needle should be held uppermost and the needle inserted into the skin somewhat beyond the bevel. The injection should be made slowly, and, when properly made, it will be followed immediately by a sharply delimited hemispherical swelling, often wheal-like, raised from 1 to 2 mm. above the surrounding skin.

The site of the injection is examined 48 hours later, and, if no reaction is noted, 0.1 cc. of a similarly-made solution of the second-strength test-tablet, containing 0.005 mgm. of the protein derivative, is injected into the skin of the opposite arm. If after 48 hours no reaction is noted at the site of either injection, the person is considered negative to tuberculin.

It may be noted that the first dose of the Purified Protein Derivative recommended, 0.000,02 mgm., is equivalent to 0.002 to 0.01 mgm. of Koch's Old Tuberculin, the strength of which, as pointed out, varies with different preparations. The second dose of 0.005 mgm. is approximately equivalent to 1.0 mgm. of Old Tuberculin.

When many persons are to be tested, especially in schools or in the countryside, the tablet equipment for large scale-testing is used. For convenience in transporting the equipment and making the test rapidly

in large groups, the arrangement shown in figure 1 has been found to be useful. In this equipment are tablets of the protein derivative, bottles containing the desired amount of sterile diluent, and an alcohol lamp, which can be readily made from a small lubricating can by shortening the top to the desired length. A can of 250-cc. capacity, containing methyl

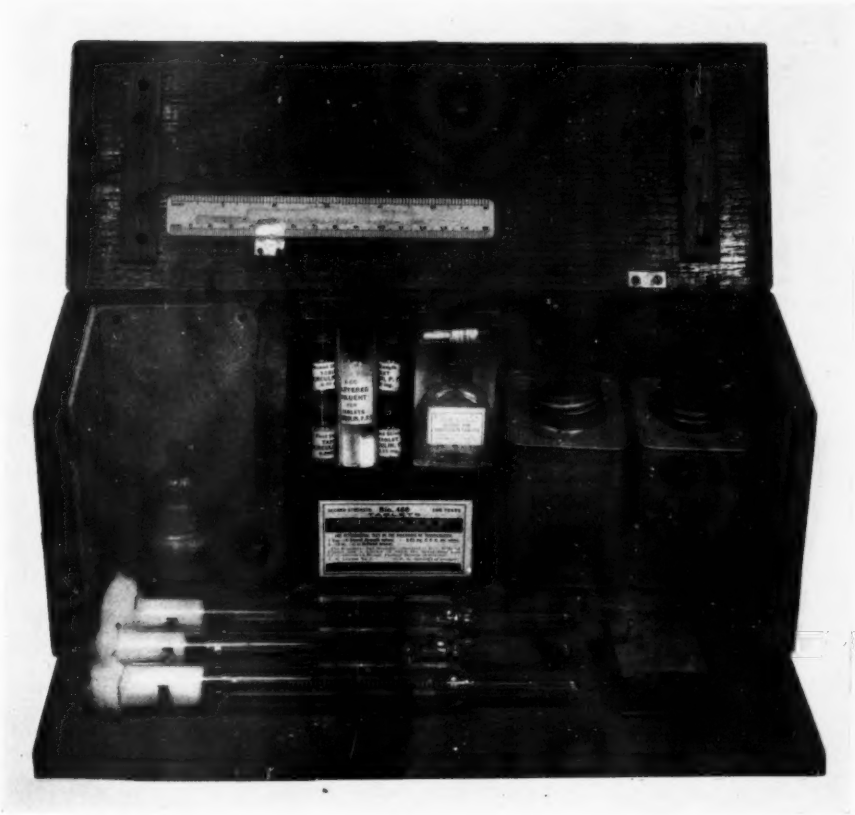

FIG. 1

alcohol for the lamp, and a can of ethyl alcohol for cleansing the arm, are attached to the floor of the box by means of suitably shaped tool holders. The hinged front of the box holds three tubes made of hard glass, measuring 170 by 20 mm., constricted at the bottom to hold the needle and flattened at the top to prevent rolling. In each of these tubes there is a 1.0-cc. tuberculin syringe and a 26-gauge platinum needle of half-inch

length covered by a metal sleeve to protect its point. The tube and syringe may be sterilized by dry heat in an oven or by boiling in water. A box of matches is also fastened to this side of the box and the cover holds a ruler used to measure the tuberculin reaction.

The inside measurements of the box are: length 13 inches, width 5 inches and height $4\frac{1}{2}$ inches. The compartment holding the alcohol lamp should be lined with transite or asbestos, and an air-space of about $\frac{1}{4}$ inch should be left between this and the wall to prevent scorching. The equipment is held in place by tool-holders which can readily be shaped for this purpose.

When injections are to be made the needle and syringe are removed from the glass tube and the stopper replaced. The metal sleeve is removed from the platinum needle, which is then heated to a dull red in the flame of the alcohol lamp and permitted to cool. The stopper is removed from the bottle of diluted tuberculin and the syringe is loaded. After an injection the needle is again heated, a drop of the solution is ejected and the test is repeated on the next person.

In order to obviate reactions due to trauma it is necessary that the needles be sharp and smooth. Since platinum needles are softer than steel, care must be taken that the point is not blunted. To prevent this possibility the platinum needle should not be inserted through thick rubber stoppers and care should be exercised in loading the syringe not to scrape the point of the needle against the bottom of the bottle.

READING AND GRADING REACTIONS

The results of the injection should be read 48 hours after the injection, at which time, in most instances, the reaction reaches its maximum. It is advisable, as a routine, to have the patient bare both forearms to make sure after the second injection whether there has been a delayed reaction to the first dose. Note is made of the area of redness, the area and height of the inflammatory oedema and the presence of lymphangitis, blanching, vesiculation, necrosis or ecchymosis. Rarely there may be some systemic reaction, such as fever, headache, backache or malaise. Severe reactions, if they occur, are always the result of the first dose. With the procedure here proposed, in which the first dose has been set at the low figure of 0.000,02 mgm., serious reactions are less likely to take place than in other procedures frequently followed in tuberculin testing.

Positive reactions may be arbitrarily classified as one, two, three or

four plus, depending upon the extent of oedema measured at its widest diameters. A reaction showing some redness and definite oedema more than 5 mm., and not exceeding 10 mm. in diameter, is recorded as a one-plus (+) reaction. A two-plus reaction (++) is an area of redness and oedema measuring from 10 to 20 mm. in diameter. A three-plus reaction (+++) is characterized by marked redness and oedema exceeding 20 mm. in diameter. A four-plus reaction (++++) consists of marked redness, oedema and an area of necrosis. A reaction with slight redness and a trace of oedema, measuring 5 mm. or less in diameter, is marked doubtful. If there is no oedema at the site of injection, even if a slight redness is present, the test is recorded as negative. In interpreting the tuberculin reaction it must be remembered that redness is of less significance than the oedema.

The system of grading just outlined is slightly modified from that previously recommended in the *Diagnostic Aids* published by the National Tuberculosis Association (6). The experience of recent years has indicated the advisability of enlarging the two-plus range to permit distinctions within the large group previously recorded as three plus.

In the more sensitive individuals the reaction may be characterized by extensive oedema with a central dark red indurated area. In some instances blanching occurs in the centre of the indurated area and in rare instances small ecchymotic areas have been noted. Lymphangitis, usually mild and transitory in nature, is frequently associated with the more severe types of reaction. In a number of cases small superficial vesicles, 1 to 2 mm. in diameter, are found. A note of such manifestations of severity of reaction should be made in the record, but, unless actual necrosis is seen, the reaction is not read as more than three plus. The more severe reactions have been found most frequently among well-nourished persons, who have been in contact with manifest tuberculosis for a considerable period of time, and they have occurred more often among Indians and Negroes than among white persons. In general they are seen more frequently in extrapulmonary than in pulmonary tuberculosis. The application of a saturated watery solution of magnesium sulphate rapidly reduces the swelling, and carbolized vaseline allays the itching which is associated with the more severe reactions.

When severe reactions have been obtained they have invariably been elicited by the first dose of the tuberculin, and we have not observed a severe reaction when 250 times the initial dose has been injected in those who failed to react to the first dose, as recommended in this series of

papers. It must be remembered that sensitiveness to tuberculin may be decreased or disappear in the course of exanthematous diseases or in the course of other diseases associated with high temperature. In all such instances, patients upon recovery should be retested with the initial dose of 0.000,02 mgm., rather than with the larger dose.

When a previous injection of tuberculin has caused a severe reaction, in retesting such a patient it is advisable to reduce the first dose of the Purified Protein Derivative to 0.000,002 mgm.; that is, one-tenth of the standard amount.

SUMMARY

1. The technique of the intracutaneous tuberculin test and interpretation of the results are described for the use of the Purified Protein Derivative, put up in the manner described in this series of papers.

2. It is recommended that the initial dose be 0.000,02 mgm. and that 0.005 mgm. be injected into the skin of those who fail to react to the first dose.

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TUBERCULIN SURVEYS WITH THE PURIFIED PROTEIN DERIVATIVE[1]

The Determination of Optimum Dosage

ESMOND R. LONG, JOSEPH D. ARONSON AND FLORENCE B. SEIBERT

In testing the potency and constancy of the Purified Protein Derivative, as made by Seibert, and establishing the optimum dosage, about three thousand tests have been made.

Preliminary trials of the potency of the product were carried out on experimental animals, and, following this, on patients in the clinic of the Henry Phipps Institute. The sample of Old Tuberculin that has been used in the Institute for the last two years was employed as a standard of comparison. This is a preparation of high activity. Table 1, selected from typical examinations by Aronson, that were made by the method of Lewis and Aronson (1), shows its potency in comparison with several preparations, all well-known and widely used. At the same time the figures demonstrate a wide variation in the activity of these preparations.

Results secured previously with other types of purified protein from tuberculin indicated that, on the average, samples of good OT are approximately equal in strength to one per cent solutions of the protein. On a guinea-pig skin-test-potency basis, Seibert and Munday (2) considered 1 gm. of tuberculin protein isolated by trichloracetic acid precipitation (TPT) biologically equivalent to 100 cc. of OT. Chemical isolation gave results in conformity, 0.7 gm. of the active protein being actually obtained from 100 cc., in spite of the losses incident to manipulation.

Accordingly, in the initial tests at the Phipps Institute and the cooperating Clinic Number 3 of the Philadelphia Health Council, the Purified Protein Derivative and the Old Tuberculin of the Institute were compared in doses respectively of 0.000,1 mgm. of the Protein Derivative and 0.01 "mgm." OT for the first injection, and 0.01 mgm. of the Protein Derivative and 1.0 "mgm." OT for the second. In these tests, and in

[1] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

TABLE 1

*Comparison of tuberculin from different sources**

BUREAU OF ANIMAL INDUSTRY	COMMERCIAL (USED AT PHIPPS INSTITUTE)	FOREIGN GOVERNMENT 1	FOREIGN GOVERNMENT 2	STATE 1
Strong	Strong	Strong	Weaker	Almost inert
GUINEA PIG NUMBER	BUREAU OF ANIMAL INDUSTRY	COMMERCIAL (USED AT PHIPPS INSTITUTE)	CITY	STATE 2
A	8 x 7 x 1	12 x 7 x 2	15 x 8 x 2	Negative
B	7 x 7 x trace	10 x 9 x 1	7 x 7 x trace	Negative
C	23 x 18 x 3(n)	20 x 12 x 3(n)	20 x 15 x 3(n)	7 x 7 x 2

(n) = necrosis.

* The upper blocks represent the summary of a series of comparative tests on tuberculins of the origin indicated. The lower blocks record a single example of such a comparative test on four different tuberculins. Three guinea pigs of different sensitivity were used. The figures are millimetre measurements of reactions to identical quantities of tuberculin from the four sources. The Bureau of Animal Industry, Commercial (used at Phipps Institute) and City products were of approximately equal strength, but the State product compared with them was very weak, causing only a weak reaction in the most sensitive guinea pig.

TABLE 2

Summarized comparison of OT (first dose 0.01 mgm.; second dose 1.0 mgm.) and Purified Protein Derivative (first dose 0.000,1 mgm.; second dose 0.01 mgm.)

Colored subjects

AGE-GROUP IN YEARS	NUMBER TESTED	POSITIVE TO 0.01 MGM. OT	POSITIVE TO 0.000,1 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO 1.0 MGM. OT	POSITIVE TO 0.01 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO OT		POSITIVE TO PURIFIED PROTEIN DERIVATIVE	
						Total	Per cent	Total	Per cent
0–4	11	7	7	0	1	7	63.6	8	72.7
5–9	23	6	6	3	5	9	39.1	11	47.8
10–14	36	15	17	3	7	18	50.0	24	66.6
15–19	7	3	5	1	0	4	57.1	5	71.4
20–69	13	12	13	1	0	13	100.0	13	100.0
Totals	90	43	48	8	13	51	56.6	61	67.8
INTENSITY OF REACTION							PERCENTAGE OF TOTAL POSITIVE		PERCENTAGE OF TOTAL POSITIVE
1+		2	3	1	3	3	5.9	6	9.8
2+		5	4	6	7	11	21.6	11	18.0
3+		35	34	1	3	36	70.5	37	60.7
4+		1	7	0	0	1	2.0	7	11.5
Totals		43	48	8	13	51	100.0	61	100.0

all subsequently, the two tuberculins under comparison were injected intracutaneously into corresponding regions of the opposite forearms.

The results of this test are summarized in table 2. The intensity of reaction was graded according to the standards given by Aronson (3). This same system of grading was used in all of the testing here recorded in tables 2 to 10 inclusive. Recently it has seemed desirable to make more distinction within the three-plus range of intensity, and in subse-

TABLE 3

Summarized comparison of OT (first dose 0.01 mgm.; second dose 1.0 mgm.) and Purified Protein Derivative (first dose 0.000,05 mgm.; second dose 0.005 mgm.)

White subjects

AGE-GROUP IN YEARS	NUMBER TESTED	POSITIVE TO 0.01 MGM. OT	POSITIVE TO 0.000,05 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO 1.0 MGM. OT	POSITIVE TO 0.005 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO OT		POSITIVE TO PURIFIED PROTEIN DERIVATIVE	
						Total	Per cent	Total	Per cent
0–4	54	4	4	7	7	11	20.4	11	20.4
5–9	60	4	3	13	15	17	28.3	18	30.0
10–14	213	90	91	36	52	126	59.1	143	67.2
15–19	200	118	117	33	43	151	75.5	160	80.0
20–79	113	62	63	18	16	80	70.8	79	70.0
Totals	640	278	278	107	133	385	60.2	411	64.2
INTENSITY OF REACTION							PERCENTAGE OF TOTAL POSITIVE		PERCENTAGE OF TOTAL POSITIVE
1+		19	19	31	45	50	13.0	64	15.6
2+		53	52	55	64	108	28.1	116	28.2
3+		202	202	21	24	223	57.9	226	55.0
4+		4	5	0	0	4	1.0	5	1.2
Totals		278	278	107	133	385	100.0	411	100.0

quent testing the slightly modified scale defined by Aronson (4) in this series of papers was used.

It is clear from these figures that the initial dose of 0.000,1 mgm. of the Purified Protein Derivative was stronger than 0.01 "mgm." OT. Moreover, it appeared unnecessarily strong in view of the size of the reactions secured. Seven patients out of 90 tested, or 11.5 per cent of the reactors, gave four-plus reactions. The measurements for the reactions are omitted to save space. Those in the three-plus range averaged about 20 per cent greater with the Purified Protein Derivative than with the OT.

It appeared probable that severe reactions could be avoided, and at the same time all reactors detected, if the dose of Purified Protein Derivative were diminished. Accordingly a second and much larger series of tests was carried out with doses of 0.000,05 mgm. (first injection) and 0.005 mgm. (second injection) of the Protein Derivative in comparison with 0.01 "mgm." and 1.0 "mgm." OT respectively. More than a thousand tests were made, in various localities, including the Phipps Institute and the Children's Hospital of Philadelphia (about 200), the

TABLE 4

Summarized comparison of OT (first dose 0.01 mgm.; second dose 1.0 mgm.) and Purified Protein Derivative (first dose 0.000,05 mgm.; second dose 0.005 mgm.)

Colored subjects

AGE-GROUP IN YEARS	NUMBER TESTED	POSITIVE TO 0.01 MGM. OT	POSITIVE TO 0.000,05 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO 1.0 MGM. OT	POSITIVE TO 0.005 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO OT		POSITIVE TO PURIFIED PROTEIN DERIVATIVE	
						Total	Per cent	Total	Per cent
0–4	44	5	4	6	2	11	25.0	6	13.7
5–9	108	20	21	8	13	28	25.9	34	31.5
10–14	91	41	40	20	25	61	67.0	65	71.5
15–19	40	27	27	7	8	34	85.0	35	87.5
20–79	107	97	97	8	9	105	98.1	106	99.1
Totals	390	190	189	49	57	239	61.3	246	63.1
INTENSITY OF REACTION							PERCENTAGE OF TOTAL POSITIVE		PERCENTAGE OF TOTAL POSITIVE
1+		8	5	18	16	26	10.8	21	8.6
2+		15	25	18	16	33	13.8	41	16.7
3+		157	154	13	25	170	71.2	179	72.7
4+		10	5	0	0	10	4.2	5	2.0
Totals		190	189	49	57	239	100.0	246	100.0

Negro Tuberculosis Clinic of the Delaware County Tuberculosis Association in Chester, Pa. (about 300), the Westchester High School in Westchester, Pa. (about 300), and Saginaw County, Michigan (about 250). The results are summarized in tables 3, 4 and 5, the results in white and colored patients being tabulated separately in tables 3 and 4 and combined in table 5.

The results were consistent throughout. At this dosage a somewhat larger percentage of positives were still obtained with the Purified Protein Derivative, although now the average dimensions of the reaction in

the positives were a little larger with OT, as shown in figure 1. The great majority of reactions were in the three-plus range, both with OT and the Purified Protein Derivative. A number of four-plus reactions (1–4 per cent) were still obtained, however, the greater number occurring with OT. These were much commoner in the colored than the white group.

Four-plus reactions are distressing, and, especially in colored people, are apt to leave permanent scars. They should be avoided if possible. It is significant that all of the four-plus reactions occurred on the first dose. Although the second dose was one hundred times the first, the

TABLE 5

Tables 3 & 4 combined

Summarized comparison of OT (first dose 0.01 mgm.; second dose 1.0 mgm.) and Purified Protein Derivative (first dose 0.000,05 mgm.; second dose 0.005 mgm.)
White and colored subjects

AGE-GROUP IN YEARS	NUMBER TESTED	POSITIVE TO 0.01 MGM. OT	POSITIVE TO 0.000,05 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO 1.0 MGM. OT	POSITIVE TO 0.005 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO OT		POSITIVE TO PURIFIED PROTEIN DERIVATIVE	
						Total	Per cent	Total	Per cent
0–79	1,030	468	467	156	190	624	60.6	657	63.8
INTENSITY OF REACTION							PERCENTAGE OF TOTAL POSITIVE		PERCENTAGE OF TOTAL POSITIVE
1+		27	24	49	61	76	12.2	85	12.9
2+		68	77	73	80	141	22.6	157	23.9
3+		359	356	34	49	393	63.0	405	61.7
4+		14	10	0	0	14	2.2	10	1.5
Totals		468	467	156	190	624	100.0	657	100.0

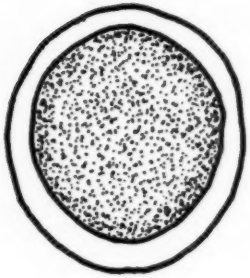
positive reactions secured, in this less sensitive group, were of considerably smaller dimensions and severity than in the more sensitive patients who reacted to the first dose. From these results it seemed probable that a still smaller initial dose might detect all of the excessively sensitive reactors, without the necrotizing reactions, and that a larger multiple than one hundred could be used with safety on the retest.

Before trying this out directly, however, it seemed an advisable precaution to begin with the initial weak dose and proceed to the usual final dose by two retests instead of one. The freshman class of 93 students at Haverford College coöperated in this trial. Of this group 87 were in

First Injection

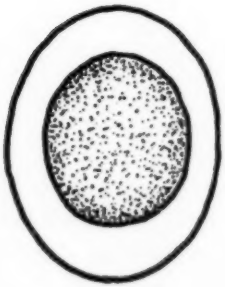
0.00005 mg.
Purified Protein
Derivative

Chester
(colored)
Average in 179
subjects

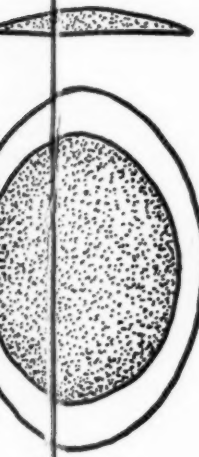
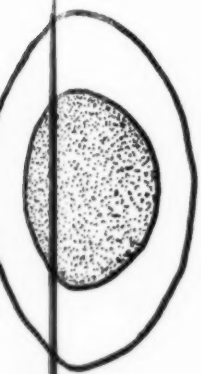


Redness 35 x 32 mm.
Swelling 29 x 27 x 3 mm.

West Chester
(white)
Average in 254
subjects



Redness 37 x 28 mm.
Swelling 22 x 19 x 2 mm.

01 mg. OT	Reinjection of Subjects Negative to First Injection 0.005 mg. Purified Protein Derivative	1.0 mg. OT
		
45 37 mm. 37 x 3 mm.	19 x 15 mm. 16 x 14 x 1 mm.	19 x 16 mm. 17 x 15 x 1 mm.
		
4 x 33 mm. 25 21 x 2 mm.	17 x 15 mm. 12 x 11 x 1 mm.	18 x 14 mm. 11 x 10 x 1 mm.

Swelling 22 x 19 x 2 mm.

TABLE 1

*Comparison of tuberculin from different sources**

BUREAU OF ANIMAL INDUSTRY	COMMERCIAL (USED AT PHIPPS INSTITUTE)	FOREIGN GOVERNMENT 1	FOREIGN GOVERNMENT 2	STATE 1
Strong	Strong	Strong	Weaker	Almost inert
GUINEA PIG NUMBER	BUREAU OF ANIMAL INDUSTRY	COMMERCIAL (USED AT PHIPPS INSTITUTE)	CITY	STATE 2
A	8 x 7 x 1	12 x 7 x 2	15 x 8 x 2	Negative
B	7 x 7 x trace	10 x 9 x 1	7 x 7 x trace	Negative
C	23 x 18 x 3(n)	20 x 12 x 3(n)	20 x 15 x 3(n)	7 x 7 x 2

(n) = necrosis.

* The upper blocks represent the summary of a series of comparative tests on tuberculins of the origin indicated. The lower blocks record a single example of such a comparative test on four different tuberculins. Three guinea pigs of different sensitivity were used. The figures are millimetre measurements of reactions to identical quantities of tuberculin from the four sources. The Bureau of Animal Industry, Commercial (used at Phipps Institute) and City products were of approximately equal strength, but the State product compared with them was very weak, causing only a weak reaction in the most sensitive guinea pig.

TABLE 2

Summarized comparison of OT (first dose 0.01 mgm.; second dose 1.0 mgm.) and Purified Protein Derivative (first dose 0.000,1 mgm.; second dose 0.01 mgm.)

Colored subjects

AGE-GROUP IN YEARS	NUMBER TESTED	POSITIVE TO 0.01 MGM. OT	POSITIVE TO 0.000,1 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO 1.0 MGM. OT	POSITIVE TO 0.01 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO OT		POSITIVE TO PURIFIED PROTEIN DERIVATIVE	
						Total	Per cent	Total	Per cent
0–4	11	7	7	0	1	7	63.6	8	72.7
5–9	23	6	6	3	5	9	39.1	11	47.8
10–14	36	15	17	3	7	18	50.0	24	66.6
15–19	7	3	5	1	0	4	57.1	5	71.4
20–69	13	12	13	1	0	13	100.0	13	100.0
Totals	90	43	48	8	13	51	56.6	61	67.8
INTENSITY OF REACTION							PERCENTAGE OF TOTAL POSITIVE		PERCENTAGE OF TOTAL POSITIVE
1+		2	3	1	3	3	5.9	6	9.8
2+		5	4	6	7	11	21.6	11	18.0
3+		35	34	1	3	36	70.5	37	60.7
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White subjects

AGE-GROUP IN YEARS	NUMBER TESTED	POSITIVE TO 0.01 MGM. OT	POSITIVE TO 0.000,05 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO 1.0 MGM. OT	POSITIVE TO 0.005 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO OT		POSITIVE TO PURIFIED PROTEIN DERIVATIVE	
						Total	Per cent	Total	Per cent
0–4	54	4	4	7	7	11	20.4	11	20.4
5–9	60	4	3	13	15	17	28.3	18	30.0
10–14	213	90	91	36	52	126	59.1	143	67.2
15–19	200	118	117	33	43	151	75.5	160	80.0
20–79	113	62	63	18	16	80	70.8	79	70.0
Totals	640	278	278	107	133	385	60.2	411	64.2
INTENSITY OF REACTION							PERCENTAGE OF TOTAL POSITIVE		PERCENTAGE OF TOTAL POSITIVE
1+		19	19	31	45	50	13.0	64	15.6
2+		53	52	55	64	108	28.1	116	28.2
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Colored subjects

AGE-GROUP IN YEARS	NUMBER TESTED	POSITIVE TO 0.01 MGM. OT	POSITIVE TO 0.000,05 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO 1.0 MGM. OT	POSITIVE TO 0.005 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO OT		POSITIVE TO PURIFIED PROTEIN DERIVATIVE	
						Total	Per cent	Total	Per cent
0–4	44	5	4	6	2	11	25.0	6	13.7
5–9	108	20	21	8	13	28	25.9	34	31.5
10–14	91	41	40	20	25	61	67.0	65	71.5
15–19	40	27	27	7	8	34	85.0	35	87.5
20–79	107	97	97	8	9	105	98.1	106	99.1
Totals	390	190	189	49	57	239	61.3	246	63.1
INTENSITY OF REACTION							PERCENTAGE OF TOTAL POSITIVE		PERCENTAGE OF TOTAL POSITIVE
1+		8	5	18	16	26	10.8	21	8.6
2+		15	25	18	16	33	13.8	41	16.7
3+		157	154	13	25	170	71.2	179	72.7
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Summarized comparison of OT (first dose 0.01 mgm.; second dose 1.0 mgm.) and Purified Protein Derivative (first dose 0.000,05 mgm.; second dose 0.005 mgm.)

White and colored subjects

AGE-GROUP IN YEARS	NUMBER TESTED	POSITIVE TO 0.01 MGM. OT	POSITIVE TO 0.000,05 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO 1.0 MGM. OT	POSITIVE TO 0.005 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO OT		POSITIVE TO PURIFIED PROTEIN DERIVATIVE	
						Total	Per cent	Total	Per cent
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INTENSITY OF REACTION							PERCENTAGE OF TOTAL POSITIVE		PERCENTAGE OF TOTAL POSITIVE
1+		27	24	49	61	76	12.2	85	12.9
2+		68	77	73	80	141	22.6	157	23.9
3+		359	356	34	49	393	63.0	405	61.7
4+		14	10	0	0	14	2.2	10	1.5
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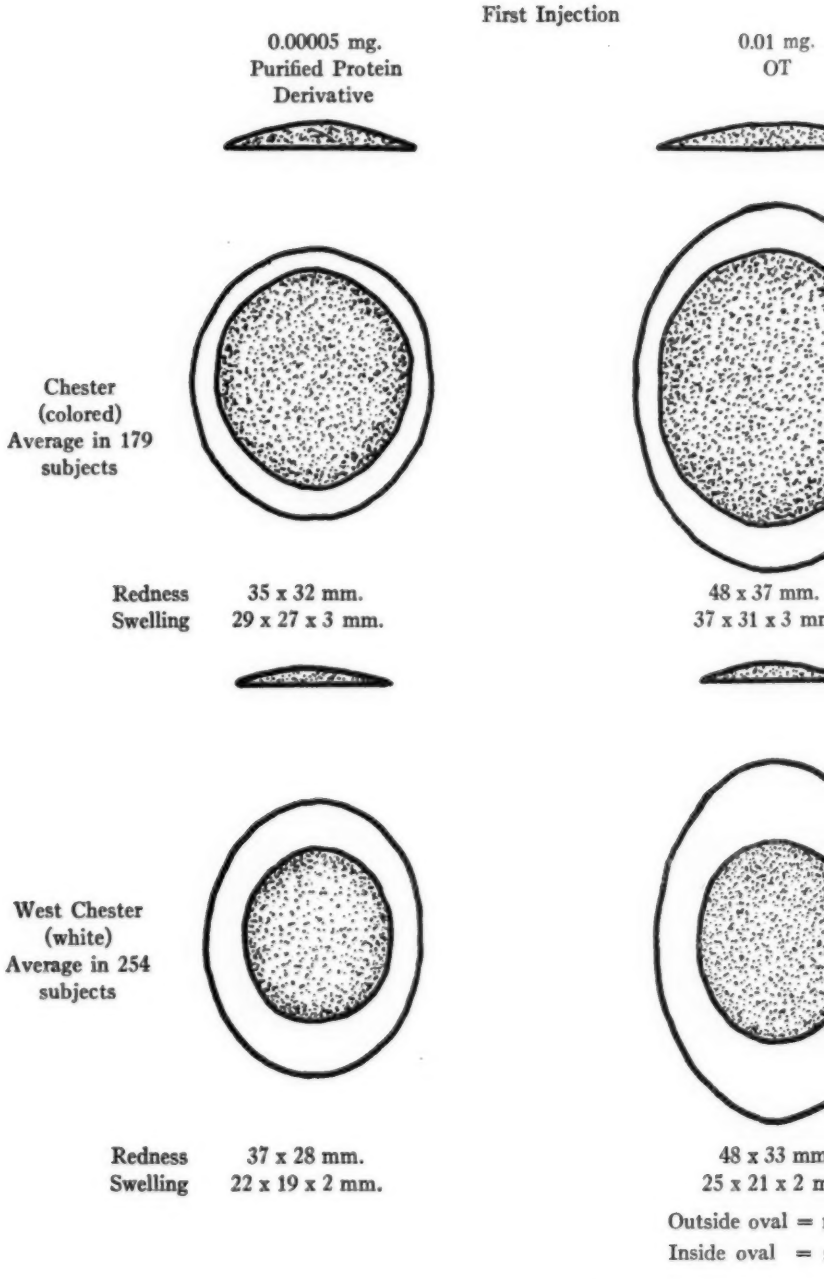
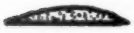
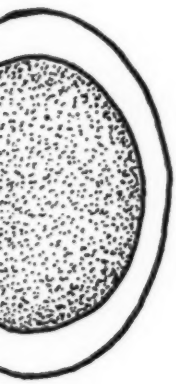
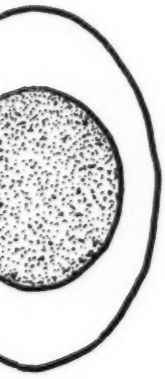


FIG. 1. COMPARISON OF REACTION TO PURIFIED PROTEIN DERIVATIVE AND O

Reinjection of
Subjects Negative to First Injection

0.01 mg. OT	0.005 mg. Purified Protein Derivative	1.0 mg. OT
		
		
x 37 mm. 31 x 3 mm.	19 x 15 mm. 16 x 14 x 1 mm.	19 x 16 mm. 17 x 15 x 1 mm.
		
x 33 mm. 21 x 2 mm.	17 x 15 mm. 12 x 11 x 1 mm.	18 x 14 mm. 11 x 10 x 1 mm.

oval = redness
oval = swelling

E AND OT. *Actual* AVERAGE SIZE OF REGIONS OF INFLAMMATION

the age-group 17–19. One boy was under 17 and five were over 20. The three successive doses injected were as follows: 0.000,02 mgm., 0.001 mgm. and 0.01 mgm. of the Purified Protein Derivative and 0.002 "mgm.," 0.1 "mgm." and 1.0 "mgm." of OT. The results are summarized in table 6.

TABLE 6

Comparison of OT (first dose 0.002 mgm.; second dose 0.1 mgm.; and third dose 1.0 mgm.) and Purified Protein Derivative (first dose 0.000,02 mgm.; second dose 0.001 mgm. and third dose 0.01 mgm.)

College freshmen

AGE-GROUP IN YEARS	NUMBER TESTED	POSITIVE TO 0.002 MGM. OT	POSITIVE TO 0.000,02 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO 0.1 MGM. OT	POSITIVE TO 0.001 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO 1.0 MGM. OT	POSITIVE TO 0.01 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO OT		POSITIVE TO PURIFIED PROTEIN DERIVATIVE	
								Total	Per cent	Total	Per cent
16–24[1]	93	35[2]	37	30[2]	31	3	2	68[2]	73.0	70	75.2
Average mm. dimensions of postive reactions		18.2 x 16.3 x 1.7	27.1 x 22.2 x 2.2	13.0 x 11.2 x 1.2	13.8 x 11.3 x 1.1	10.3 x 10.0 x 1.0	11.0 x 11.0 x 1.0				
INTENSITY OF REACTION									PERCENTAGE OF TOTAL POSITIVE		PERCENTAGE OF TOTAL POSITIVE
1+		6[2]	4	13[2]	11	3	1	22	32.3	16	22.9
2+		14	7	13	15	0	1	27	39.7	23	32.9
3+		14	25	4	5	0	0	18	26.5	30	42.8
4+		1	1	0	0	0	0	1	1.5	1	1.4
Totals		35[2]	37	30[2]	31	3	2	68[2]	100.0	70	100.0

[1] Eighty-seven of the 93 were in the age-group, 17–19.

[2] In these figures are included as positive four cases in which the reaction was ± at a low dose and a higher dose was not given. Presumably the next higher dosage would have elicited a positive reaction. In these cases the higher dose with OT was omitted because the reaction to the Purified Protein Derivative was already positive.

The significant results were as follows: The Purified Protein Derivative elicited a higher percentage of reactions than did OT. Moreover the reactions to the former were more intense, a considerably larger percentage being in the three-plus range on the first dose. There were more uncertain reactions with the OT. One highly sensitive student gave a

four-plus reaction even to 0.000,02 mgm. Purified Protein Derivative and 0.002 "mgm." OT. It is fortunate he did not receive a larger dose.

X-ray examinations of all the positive reactors were made by Dr. McPhedran and Dr. Hetherington at the Henry Phipps Institute. In 37 no tuberculosis could be detected. In seven there was apical infiltration of suspected tuberculous origin. It is interesting that the two students who reacted only to the last dose of Purified Protein Derivative were in this group. Of these seven, only one had a lesion of sufficient gravity to merit an altered schedule of activity. His reaction was three-plus to both tuberculins. In 15 students apical infiltration was suspected only. The student giving a four-plus reaction was in this group. The remaining students had childhood nodules in the lungs or lymph nodes, which were considered of no clinical significance. No further analysis of the X-ray data will be reported, as no correlation between X-ray findings and intensity of tuberculin reaction was noted.

Inasmuch as all but two of the 70 positive reactions to the Purified Protein Derivative were obtained with the first two test dosages it was thought probable that a final dose, one-half as large as the third test dose, would be practically as effective, and that the middle dose might be omitted entirely. This procedure seemed safe, also, in view of the fact that the reactions to the second dose were smaller than those to the first. This would mean starting with 0.000,02 mgm. of the Purified Protein Derivative and multiplying this dose two hundred and fifty times on the retest of those not reacting to the first dose.

The opportunity for this trial was presented in the course of a tuberculin and X-ray survey at a neighboring detention school, an institution housing white and colored boys. About 500 boys were to be tested, a number permitting grouping for several trials on dosage. In one group of 109 a test was made of the proposed two-dose method, starting with 0.000,02 mgm. of the Purified Protein Derivative and closing with 0.005 mgm. on the nonreactors to the first dose. The test was controlled by OT in doses of 0.004 and 1.0 "mgm.," respectively, on the opposite arm. The initial dose of OT was thus twice that used in the preceding test and the final dose of the Purified Protein Derivative half of that used in that test. With each tuberculin, the second dose was two hundred and fifty times the size of the first. The results are summarized in table 7.

A slightly larger percentage reacted to the Purified Protein Derivative than to the OT in both the white and colored groups. It is noteworthy that in the colored group a higher percentage of the total reactors reacted

to the first dose than was the case in the white group. This is in accord with our general experience at the Phipps Institute. Illustrations of this phenomenon will be seen in later tables. The intensity of reaction, on the average in the combined groups, was greater with the Purified

TABLE 7

Summarized comparison of OT (first dose 0.004 mgm.; second dose 1.0 mgm.) and Purified Protein Derivative (first dose 0.000,02 mgm.; second dose 0.005 mgm.)

AGE-GROUP IN YEARS	NUMBER TESTED	POSITIVE TO 0.004 MGM. OT	POSITIVE TO 0.000,02 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO 1.0 MGM. OT	POSITIVE TO 0.005 MGM. PURIFIED PROTEIN DERIVATIVE	POSITIVE TO OT		POSITIVE TO PURIFIED PROTEIN DERIVATIVE	
						Total	Per cent	Total	Per cent
White									
10–14	24	4	5	8	9	12	50.0	14	58.3
15–19	54	16	18	14	12	30	55.5	30	55.5
Totals	78	20	23	22	21	42	53.8	44	56.4
Colored									
10–14	8	6	7	1	0	7	87.5	7	87.5
15–19	23	14	15	1	2	15	65.2	17	73.9
Totals	31	20	22	2	2	22	70.9	24	77.4
Total white and colored	109	40	45	24	23	64	58.7	68	62.4
Average mm. dimensions of positive reactions		13.6 x 12.0 x 2.1	17.0 x 14.3 x 2.8	13.4 x 12.0 x 1.3	12.5 x 10.2 x 1.4				
INTENSITY OF REACTION							PERCENTAGE OF TOTAL POSITIVE		PERCENTAGE OF TOTAL POSITIVE
1+		12	6	8	9	20	31.2	15	22.1
2+		22	15	12	8	34	53.1	23	33.8
3+		6	24	4	6	10	15.7	30	44.1
Totals		40	45	24	23	64	100.0	68	100.0

Protein Derivative than with the OT; as table 7 shows, with the former a larger proportion of the reactions were in the three-plus range (44.1 as compared with 15.7 per cent). No four-plus reactions occurred.

As the Purified Protein Derivative incorporated in tablet form, prepared as described by Reichel and Clark (5), had just become available

at the time of this test, a comparison of this material with OT was made on three other groups of the boys from this school. Three groups were used because it was desired to test the tablets against three different first-dose tests of OT, namely, 0.002, 0.004 and 0.01 "mgm.".

TABLE 8

Summarized comparison of OT (first dose 0.004 mgm.; second dose 1.0 mgm.) and Purified Protein Derivative in tablets (first dose 0.000,02 mgm.; second dose 0.005 mgm.)

AGE-GROUP IN YEARS	NUMBER TESTED	POSITIVE TO 0.004 MGM. OT	POSITIVE TO 0.000,02 MGM. PURIFIED PROTEIN DERIVATIVE IN TABLET	POSITIVE TO 1.0 MGM. OT	POSITIVE TO 0.005 MGM. PURIFIED PROTEIN DERIVATIVE IN TABLET	POSITIVE TO OT		POSITIVE TO PURIFIED PROTEIN DERIVATIVE IN TABLET	
						Total	Per cent	Total	Per cent
White									
10–14	3	0	0	2	2	2	66.6	2	66.6
15–19	20	8	7	3	2	11	55.0	9	45.0
Totals	23	8	7	5	4	13	56.5	11	47.8
Colored									
5–9	6	2	2	0	0	2	33.3	2	33.3
10–14	48	22	21	7	7	29	60.4	28	58.3
15–19	33	16	15	5	6	21	63.6	21	63.6
Totals	87	40	38	12	13	52	59.8	51	58.7
Total white and colored	110	48	45	17	17	65	59.1	62	56.4
Average mm. dimensions of positive reactions		16.3 x 14.4 x 2.4	14.5 x 13.4 x 2.7	18.5 x 14.9 x 1.8	14.7 x 12.9 x 1.7				
INTENSITY OF REACTION							PERCENTAGE OF TOTAL POSITIVE		PERCENTAGE OF TOTAL POSITIVE
1+		7	8	0	7	7	10.8	15	24.2
2+		24	22	9	6	33	50.8	28	45.2
3+		17	15	8	4	25	38.4	19	30.6
Totals		48	45	17	17	65	100.0	62	100.0

Since this was the first time tablets with the Purified Protein Derivative had been manufactured, and certain technical difficulties had not yet been overcome, the tests cannot be considered of the same significance as those made with tablets of later manufacture. The tablets of

first manufacture were made up on the basis of 0.001 mgm. and 0.1 mgm. Purified Protein Derivative per tablet. In order to secure the desired test doses these tablets were dissolved in buffered saline solution in such

TABLE 9

Summarized comparison of OT (first dose 0.002 mgm.; second dose 0.5 mgm.) and Purified Protein Derivative in tablets (first dose 0.000,02 mgm.; second dose 0.005 mgm.)

AGE-GROUP IN YEARS	NUMBER TESTED	POSITIVE TO 0.002 MGM. OT	POSITIVE TO 0.000,02 MGM. PURIFIED PROTEIN DERIVATIVE IN TABLET	POSITIVE TO 0.5 MGM. OT	POSITIVE TO 0.005 MGM. PURIFIED PROTEIN DERIVATIVE IN TABLET	POSITIVE TO OT		POSITIVE TO PURIFIED PROTEIN DERIVATIVE	
						Total	Per cent	Total	Per cent
White									
10–14	17	3	3	4	3	7	41.2	6	35.3
15–19	161	58	61	45	30	103	63.97	91	56.5
20–24	3	0	0	0	0	0	0.0	0	0.0
Totals	181	61	64	49	33	110	60.8	97	53.6
Colored									
10–14	19	10	11	3	1	13	68.4	12	63.16
15–19	41	20	19	8	6	28	68.3	25	60.97
20–24	1	1	1	0	0	1	100.0	1	100.0
Totals	61	31	31	11	7	42	68.85	38	62.3
Total white and colored	242	92	95	60	40	152	62.8	135	55.8
Average mm. dimensions of positive reactions		11.3 x 10.3 x 1.5	13.2 x 10.3 x 1.5	15.8 x 13.7 x 1.6	15.3 x 13.7 x 1.9				
INTENSITY OF REACTION							PERCENTAGE OF TOTAL POSITIVE		PERCENTAGE OF TOTAL POSITIVE
1+		51	27	17	16	68	44.8	43	31.9
2+		35	53	26	13	61	40.1	66	48.9
3+		6	15	17	11	23	15.1	26	19.2
Totals		92	95	60	40	152	100.0	135	100.0

dilution as to produce the required dose in 0.1 cc. Tables 8 and 9 summarize comparisons of the "tableted" material and OT in different dosages in two of the three groups.

The results were somewhat disquieting when first secured, because for

the first time the Purified Protein Derivative elicited a smaller number of positive reactions than the standardized OT used. Analysis of the figures brought out two important facts, however. In the first place the majority of the loss occurred on the second dose; that is, among the less highly sensitized subjects not reacting to the first-dose tests. Second, the largest loss occurred in the white boys 15–19 years of age, and more detailed examination of the records showed that within this group the major por-

TABLE 10

Summarized comparison of OT (first dose 0.01 mgm.; second dose 1.0 mgm.) and Purified Protein Derivative in tablets (first dose, 0.000,1 mgm.; second dose, 0.01 mgm.)

AGE-GROUP IN YEARS	NUMBER TESTED	POSITIVE TO 0.01 MGM. OT	POSITIVE TO 0.000,1 MGM. PURIFIED PROTEIN DERIVATIVE IN TABLET	POSITIVE TO 1.0 MGM. OT	POSITIVE TO 0.01 MGM. PURIFIED PROTEIN DERIVATIVE IN TABLET	POSITIVE TO OT		POSITIVE TO PURIFIED PROTEIN DERIVATIVE IN TABLET	
						Total	Per cent	Total	Per cent
White									
5–9	4	2	2	0	0	2	50.0	2	50.0
10–14	41	4	4	5	6	9	21.9	10	24.4
15–19	2	1	1	0	0	1	50.0	1	50.0
Totals	47	7	7	5	6	12	25.5	13	27.6
Average mm. dimensions of positive reactions		17.7 x 14.9 x 2.3	22.0 x 17.3 x 3.0	14.0 x 12.2 x 1.0	16.3 x 13.8 x 1.5				
INTENSITY OF REACTION							PERCENTAGE OF TOTAL POSITIVE		PERCENTAGE OF TOTAL POSITIVE
1+		1	2	2	1	3	25.0	3	23.1
2+		2	4	1	2	3	25.0	6	46.2
3+		4	1	2	3	6	50.0	4	30.7
Totals		7	7	5	6	12	100.0	13	100.0

tion of the loss occurred within the inmates of two particular cottages, who happened to be first in line on the day of testing. It therefore seemed probable that the Purified Protein Derivative, under the new conditions of tablet manufacture, was not completely in solution at the beginning of the test. In all subsequent testing care was taken against this danger. When larger dosages of the Purified Protein Derivative were used in the same manner in a test made on the same day in another

group of boys, no deficiency of reactions with the tablets occurred (see table 10).

X-ray examinations were reassuring in making it clear that no cases of tuberculosis of clinical significance were included in the 20 subjects who reacted to OT and not to the tablets of Purified Protein Derivative. In fact in only one was any lesion whatsoever seen (patient no. 24, table 12). Out of 508 tested with tuberculin 298 reacted positively. These, with two or three exceptions, together with 35 not reacting to tuberculin, were X-rayed. The X-ray examinations were made by Dr. Paul B. Kreitz of the Philadelphia Health Council and Tuberculosis Committee. The data given in tables 11 and 12 are taken from his report.

The results summarized in the tables include those secured with both the "tableted" and "untableted" Purified Protein Derivative. The agreement between the two tuberculins used is almost perfect. Only

TABLE 11

Total number of pupils examined	330
Total number with tuberculous lesions (all types)	54
Soft pulmonary infiltration (active)	1
Nonapical strand-like pulmonary infiltrations	4
Apical infiltrations	2
Pulmonary nodules	19
Uncalcified or partially calcified tracheobronchial lymph nodes	4
Calcification of tracheobronchial lymph nodes	24
	54

two significant discrepancies between the two occur; namely, in the cases of patients no. 24 and no. 45. Patient no. 24 of table 12 was one of the twenty who reacted to OT and not to the Purified Protein Derivative. In his case the reaction to the former was only one-plus to the second dose. Obviously his sensitiveness was of low degree. The other nineteen were negative by X-ray. It may be noted in passing that eight of these gave one-plus reactions, nine gave two-plus reactions and two of them three-plus reactions. Patient no. 45 on the other hand reacted on the first dose to the Purified Protein Derivative, and was negative to OT on both doses. Two patients with X-ray changes diagnosed as tuberculous (nos. 27 and 46) were negative to both doses of both tuberculins. The diagnosis might be questioned in the case of no. 27. It is well known, on the other hand, that patients with thoroughly calcified lesions, like no. 46, may be negative to tuberculin.

TABLE 12

Tuberculin reactions

X-RAY DIAGNOSIS	PATIENT NUMBER	OT		PURIFIED PROTEIN DERIVATIVE	
		1st dose	2nd dose	1st dose	2nd dose
Soft pulmonary infiltration (active)	1	3+		2+	
Nonapical strand-like pulmonary infiltration	2	0	2+	0	1+
	3	1+		1+	
	4	0	1+	0	1+
	5	3+		3+	
Apical infiltration	6	1+		1+	
	7	1+		1+	
Pulmonary nodules	8	0	2+	0	3+
	9	1+		1+	
	10	0	2+	0	2+
	11	0	3+	0	2+
	12	0	2+	0	3+
	13	3+		3+	
	14	3+		3+	
	15	3+		3+	
	16	1+		1+	
	17	1+		2+	
	18	0	1+	0	1+
	19	1+		2+	
	20	2+		2+	
	21	1+		2+	
	22	0	3+	0	2+
	23	2+		1+	
	24	0	1+	0	0
	25	1+		3+	
	26	1+		2+	
Uncalcified or partially calcified tracheobronchial lymph nodes	27	0	0	0	0
	28	1+		2+	
	29	3+		3+	
	30	3+		3+	
Calcification of tracheobronchial lymph nodes	31	2+		3+	
	32	2+		2+	
	33	1+		1+	
	34	2+		2+	
	35	1+		2+	
	36	0	3+	0	3+
	37	2+		2+	
	38	3+		3+	

TABLE 12—*Concluded*

X-RAY DIAGNOSIS	PATIENT NUMBER	OT		PURIFIED PROTEIN DERIVATIVE	
		1st dose	2nd dose	1st dose	2nd dose
Calcification of tracheobronchial lymph nodes—*Concluded*	39	3+		3+	
	40	2+		2+	
	41	0	3+	0	1+
	42	1+		1+	
	43	2+		2+	
	44	2+		3+	
	45	0	0	2+	
	46	0	0	0	0
	47	3+		2+	
	48	1+		1+	
	49	2+		2+	
	50	1+		1+	
	51	1+		1+	
	52	0	2+	0	2+
	53	0	0	0	0
	54	0	3+	0	3+

It is worth adding for its general interest that, throughout the series, and in both the 10–14 and 15–19 age-groups (with one exception when an age-group had only three white and six colored representatives), the incidence of positive reactions was higher in the colored than the white children. This is in conformity with our general experience at the Phipps Institute, indicating that in the communities under consideration primary tuberculous infection occurs on a more extended scale in the younger age-groups in the colored than in the white race.

Opportunity for a second large trial of the "tableted" Purified Protein Derivative in comparison with OT was afforded in the pupil body of an orphan school in San Juan, Puerto Rico, through arrangements made by Dr. J. Rodríguez Pastor, Chief of the Bureau of Tuberculosis in the Department of Health, and with the coöperation of Dr. P. Morales Otero of the School of Tropical Medicine. By this time conditions of tablet manufacture were standardized as outlined by Reichel and Clark (5). Dr. Rodríguez Pastor was in the habit of using first and second doses of 0.1 and 1.0 "mgm.," respectively, of a certain commercial brand of OT. He stated that while infection incidence was high, the level of tuberculin sensitiveness in the community was relatively low, and that unduly severe reactions with 0.1 "mgm." of OT of the commercial brand used, did not occur. For his purposes it was desirable to compare his material

and dosages, not only with the Purified Protein Derivative, but also with the standardized OT long in use at the Phipps Institute, and employed as the standard OT for comparison in the whole series of comparative tests here recorded. Accordingly two groups of pupils were set up. Each group was tested with Purified Protein Derivative in tablets, with first and second doses of 0.000,02 mgm. and 0.005 mgm., but one group received 0.1 "mgm." of Dr. Rodríguez Pastor's OT for the first dose, and the other 0.01 "mgm." of the Phipps Institute OT. In both groups the second dose of OT was 1.0 "mgm."

Three hundred and eighteen boys were tested, including 236 recorded as white and 82 as mulatto or black. Separate records were kept for the white and colored, but analysis of the results indicated practically no difference in response to tuberculin in the two groups, and hence there is no point in putting separate tables on record.

It also appears unnecessary to separate, in the table here presented, the differences occurring on first injection of the different preparations of OT in the dosages of 0.1 and 0.01 "mgm." As might be expected, the first test reactions were somewhat more severe with the 0.1 than the 0.01 "mgm." The larger number of reactions occurred in the three-plus range in the group tested with 0.1 "mgm." OT and in the two-plus range in the group tested with 0.01 "mgm." of the other OT. Otherwise the two preparations of OT behaved similarly.

The results of the comparison in summarized form are presented in table 13. For the first time the new scale of reading (4) was used. Because the first-test strength of the OT's used was relatively strong, special attention was devoted to the incidence of severe reactions. However no four-plus reactions occurred. As Dr. Rodríguez Pastor had said, tuberculin sensitiveness in the community, in spite of the high incidence of infection, was not high. A number of reactions with vesiculation took place, but as there was no true necrosis, these were recorded as three-plus. For their interest they are indicated separately in the table, however.

Summarizing the results, we note that the first injection of OT, in the relatively large doses of 0.1 and 0.01 "mgm.," caught a larger percentage of positive reactors than the "tableted" Purified Protein Derivative. The difference was almost made up on the second injections, however, the final figures being only 2.5 per cent apart, with the OT still eliciting a slightly larger percentage of reactions. Because of the relatively large first dose of OT the highest proportion of the positive reactions occurred

in the three-plus range. With the Purified Protein Derivative, of which the low initial dose of 0.000,02 mgm. was employed, the highest proportion of positives gave two-plus reactions. The distribution of reactions by intensity with the Protein Derivative (9 per cent at one-plus, 50 per cent at two-plus and 41 per cent at three-plus, with no four-plus reactions, and only 3 per cent of severe three-plus reactions) was considered satisfactory from the standpoint of minimization of inconvenience to the subjects tested.

TABLE 13

Comparison of OT (first dose 0.01 or 0.1 mgm.; second dose 1.0 mgm.) and Purified Protein Derivative tablets (first dose 0.000,02 mgm.; second dose 0.005 mgm.)

White and colored subjects

AGE-GROUP IN YEARS	NUMBER TESTED	POSITIVE TO 0.01 OR 0.1 MGM. OT	POSITIVE TO 0.000,02 MGM. PURIFIED PROTEIN DERIVATIVE IN TABLET	POSITIVE TO 1.0 MGM. OT	POSITIVE TO 0.005 MGM. PURIFIED PROTEIN DERIVATIVE IN TABLET	POSITIVE TO OT		POSITIVE TO PURIFIED PROTEIN DERIVATIVE IN TABLET	
						Total	Per cent	Total	Per cent
5–9	22	14	11	0	4	14	63.6	15	68.2
10–14	180	127	115	21	27	148	62.2	142	78.9
15–19	116	94	84	13	20	107	92.2	104	89.7
Totals	318	235	210	34	51	269	84.6	261	82.1
INTENSITY OF REACTION							PERCENTAGE OF TOTAL POSITIVE		PERCENTAGE OF TOTAL POSITIVE
1+		3	12	5	11	8	2.9	23	8.8
2+		107	111	17	19	124	46.1	130	49.8
3+		116	80	10	20	126	47.0	100	38.3
3+ with slight vesiculation		9	7	2	1	11	4.0	8	3.1
Totals		235	210	34	51	269	100.0	261	100.0

Subsequent tests in large number, in Philadelphia, have substantially reproduced the figures of table 13. These tests, therefore, need not be recorded here. It will be worth while to add, however, two tables bearing on the reliability of tablet manufacture. Tables 14 and 15 indicate the degree of correlation that may be expected between the reactions to "tableted and untableted" Purified Protein Derivative when tested simultaneously in identical dosage on opposite forearms. In the cases summarized in table 14, first-dose tablets and a sample of the Purified

Protein Derivative from which they were compounded were compared in a group of colored patients in Clinic No. 3 of the Philadelphia Health Council. In table 15 the results with second-dose tablets from one of the coöperating biological supply houses and identical dosages of Purified Protein Derivative made in the laboratory of the Phipps Institute are compared. The tests were made on white and colored patients in the Phipps Institute. These tables do not represent selected experiments, but ordinary routine tests. The reactions are recorded in the order in which the patients entered the clinic. Many similar series could be reported.

It should be noted that repeated tests on blank lactose tablets, carried out in exactly the same manner as the tests on tablets containing Purified Protein Derivative, have never caused a reaction in either a tuberculous or nontuberculous subject.

Eight tablets taken at random from a large shipment, and numbered 1 to 8, were studied in the series reported in table 14. From four to six tests were made with each tablet. In general the reactions were slightly weaker to the Purified Protein Derivative in "tableted" than in "untableted" form. There were no discrepancies as respects positive and negative reactions. In general, too, when the reaction was strong or weak to the tuberculin in either form it was strong or weak to the tuberculin in the other form. For the comparison desired, the average dimensions of the positive reactions with each tablet are more significant than the individual positive tests. Differences in individual reactions, such as those recorded in the case of tablet 1, must depend on individual differences in the tests on the two arms, and not on the character of the tablet, since the discrepancies noted are not all in the same direction. The average measurements of the positive reactions are very close for the tuberculin in the two forms. For example in the case of patients tested with tablet 1 the average level of sensitiveness to tuberculin was high, while in the case of those tested with tablet 4 the average level of sensitiveness was relatively low. The difference in degree of sensitiveness is apparent with tuberculin in each form, even though the dimensions of the reactions are not identical.

The same trends are seen in the summary in table 15, in which "untableted" Purified Protein Derivative and tablets of the substance made up for second-test dosage are compared. In this series one discrepancy as respects positive and negative reactions occurred; namely, patient 4 tested with tablet 4, who reacted weakly to the "untableted" and not to

TABLE 14

Comparison of Purified Protein Derivative as solution of untableted powder and as solution of tablets of first-test strength (0.000,2 mgm. per tablet; 0.000,02 mgm. per dose)

PATIENT NUMBER	MEASUREMENTS (MM.) OF REACTION TO SOLUTION OF UNTABLETED POWDER		MEASUREMENTS (MM.) OF REACTION TO SOLUTION OF TABLETS	
	Tablet 1			
1	neg.		neg.	
2	neg.		neg.	
3	45 x 40 x 3	3+	68 x 44 x 4	3+
4	neg.		neg.	
5	45 x 25 x 3	3+	35 x 20 x 4	3+
6	35 x 25 x 4	3+	25 x 23 x 4	3+
Average of positives....	41.7 x 30.0 x 3.3		42.7 x 29.0 x 4.0	
	Tablet 2			
1	neg.		neg.	
2	15 x 13 x 3	2+	30 x 25 x 4	3+
3	neg.		neg.	
4	neg.		neg.	
5	55 x 52 x 3	3+	45 x 33 x 2	3+
6	neg.		neg.	
Average of positives....	35.0 x 32.5 x 3.0		37.5 x 29.0 x 3.0	
	Tablet 3			
1	neg.		neg.	
2	70 x 35 x 6	3+	55 x 40 x 4	3+
3	18 x 16 x 3	2+	14 x 12 x 3	2+
4	neg.		neg.	
5	25 x 25 x 4	3+	20 x 20 x 3	3+
6	45 x 35 x 3	3+	55 x 35 x 4	3+
Average of positives....	39.5 x 27.7 x 4.0		36.0 x 26.7 x 3.5	
	Tablet 4			
1	30 x 25 x 3	3+	25 x 20 x 3	3+
2	25 x 15 x 3	3+	12 x 11 x 2	2+
3	30 x 28 x 2	3+	19 x 17 x 1	2+
4	neg.		neg.	
5	20 x 15 x 2	2+	15 x 13 x 2	2+
6	17 x 15 x 2	2+	20 x 17 x 2	2+
Average of positives....	24.4 x 19.6 x 2.4		18.2 x 15.6 x 2.0	

TABLE 14—*Concluded*

PATIENT NUMBER	MEASUREMENTS (MM.) OF REACTION TO SOLUTION OF UNTABLETED POWDER		MEASUREMENTS (MM.) OF REACTION TO SOLUTION OF TABLETS	
	Tablet 5			
1	38 x 35 x 4	3+	35 x 35 x 4	3+
2	13 x 12 x 1	2+	15 x 12 x 1	2+
3	40 x 32 x 5	3+	45 x 45 x 5	3+
4	50 x 42 x 6	3+	48 x 40 x 6	3+
Average of positives....	35.2 x 30.2 x 4.0		35.7 x 33.0 x 4.0	
	Tablet 6			
1	neg.		neg.	
2	17 x 15 x 1	2+	15 x 15 x 1	2+
3	25 x 19 x 2	3+	19 x 16 x 1	2+
4	neg.		neg.	
Average of positives....	21.0 x 17.0 x 1.5		17 x 15.5 x 1.0	
	Tablet 7			
1	17 x 16 x 3	2+	60 x 35 x 5	3+
2	60 x 55 x 5	3+	45 x 40 x 4	3+
3	neg.		neg.	
4	neg.		neg.	
5	24 x 20 x 3	3+	50 x 35 x 4	3+
6	neg.		neg.	
Average of positives....	33.6 x 30.3 x 3.7		51.7 x 36.7 x 4.3	
	Tablet 8			
1	neg.		neg.	
2	neg.		neg.	
3	16 x 13 x 1	2+	16 x 13 x 1	2+
4	35 x 30 x 4	3+	15 x 15 x 1	2+
5	neg.		neg.	
6	28 x 20 x 3	3+	22 x 20 x 3	3+
Average of positives....	26.3 x 21.0 x 2.7		17.7 x 16.0 x 1.7	

the "tableted" material. Such discrepancies have been seen occasionally in our large series of tests with the "tableted" material. They cannot be attributed to failure of incorporation of the Purified Protein Derivative in the tablet, because no inactive tablets have been encountered. In the case of tablet 4, patients 1 and 2 reacted to the tuberculin in this tablet with exactly the same intensity as to the "untableted" powder.

TABLE 15

Comparison of Purified Protein Derivative as solution of untableted powder and as solution of tablets of second-test strength (0.05 mgm. per tablet; 0.005 mgm. per dose)

PATIENT NUMBER	MEASUREMENTS (MM.) OF REACTION TO SOLUTION OF UNTABLETED POWDER		MEASUREMENTS (MM.) OF REACTION TO SOLUTION OF TABLETS	
	Tablet 1			
1	13 x 11 x 2	2+	15 x 14 x 2	2+
2	19 x 17 x 3	2+	18 x 15 x 3	2+
3	29 x 24 x 4	3+	29 x 25 x 5	3+
Average of positives....	20.3 x 17.3 x 3		20.7 x 18.0 x 3.3	
	Tablet 2			
1	17 x 16 x 3	2+	21 x 19 x 3	3+
2	21 x 19 x 3	3+	32 x 28 x 4	3+
3	9 x 7 x 1	1+	10 x 9 x 1	1+
Average of positives....	15.7 x 14.0 x 2.3		21.0 x 18.7 x 2.7	
	Tablet 3			
1	20 x 20 x 3	3+	10 x 8 x 1	1+
2	38 x 27 x 4 (n)	4+	28 x 23 x 4 (n)	4+
3	60 x 35 x 3	3+	20 x 18 x 3	2+
4	neg.		neg.	
5	neg.		neg.	
Average of positives....	39.3 x 27.3 x 3.3		19.3 x 16.3 x 2.7	
	Tablet 4			
1	19 x 17 x 3	2+	20 x 16 x 3	2+
2	19 x 16 x 3	2+	18 x 16 x 3	2+
3	neg.		neg.	
4	10 x 10 x 1	1+	neg.	
5	neg.		neg.	
6	neg.		neg.	
Average of positives....	16.0 x 14.3 x 2.3		19.0 x 16.0 x 3.0	
	Tablet 5			
1	9 x 7 x 1	1+	9 x 8 x 1	1+
2	12 x 11 x 2	2+	18 x 17 x 2	2+
3	13 x 12 x 2	2+	24 x 21 x 3	3+
4	neg.		neg.	
Average of positives....	11.3 x 10.0 x 1.7		17.0 x 15.3 x 2.0	

TABLE 15—*Concluded*

PATIENT NUMBER	MEASUREMENTS (MM.) OF REACTION TO SOLUTION OF UNTABLETED POWDER		MEASUREMENTS (MM.) OF REACTION TO SOLUTION OF TABLETS	
	Tablet 6			
1	14 x 13 x 2	2+	13 x 12 x 2	2+
2	19 x 16 x 3	2+	18 x 16 x 3	2+
3	neg.		neg.	
4	neg.		neg.	
Average of positives....	16.5 x 14.5 x 2.5		15.5 x 14.0 x 2.5	
	Tablet 7			
1	8 x 7 x 1	1+	14 x 12 x 2	2+
2	19 x 17 x 4	2+	21 x 18 x 4	2+
3	18 x 17 x 3	2+	15 x 10 x 3	2+
Average of positives....	15.0 x 13.7 x 2.7		16.7 x 13.3 x 3	

The occasional discrepancies have occurred almost invariably on the second dose in subjects only feebly positive to "untableted" Purified Protein Derivative or strong preparations of OT. Significant discrepancies are never seen between the "tableted" and "untableted" material in patients with well-marked sensitiveness to tuberculin. Reactions of two-plus or three-plus grade to the one are usually of corresponding intensity to the other. In the rare case in which a four-plus reaction occurs, as in patient 2 tested with tablet 3, the reaction has been four plus to both.

As a result of these tests it has been decided to accept the dosages of the Purified Protein Derivative as recorded in tables 13 to 15 as satisfactory: that is, 0.000,02 mgm. for the first dose and 0.005 mgm. for the second dose in those negative to the first dose. Unduly severe reactions appear to be ruled out. Such discrepancies as those referred to in the preceding paragraph occur only in patients of low sensitiveness; namely, those giving only one-plus reactions to the first dose of OT or not reacting to the first dose of any tuberculin. Inasmuch as the significance of these marginal reactions is still debatable, it has been decided to make no changes at present in the dosages and administration of the Purified Protein Derivative in the effort to bring them out. Effective minute dosage, with presumable corresponding elimination of nonspecific material of unknown effect in the tuberculin, and great convenience of administration, are great advantages of the material in the form and dosage recommended, which seem to outweigh these doubtfully significant losses.

SUMMARY

The potency, uniformity and general reliability of the Purified Protein Derivative have been established on the basis of about three thousand tests in comparison with a single lot of highly potent Old Tuberculin of known value.

In the course of these tests initial doses of 0.000,1, 0.000,05 and 0.000,02 mgm. of the Purified Protein Derivative were tried. The smallest of these was found most satisfactory in that it detected a high percentage of total positive reactors, with a minimum of severe reactions. A second and final dose of 0.005 mgm. of the Purified Protein Derivative was found to detect all of the remaining positive reactors to doses of 0.01 "mgm." and 1.0 "mgm." of the highly potent Old Tuberculin used. Although this dose is two hundred and fifty times the first dose, it never caused severe reactions in subjects of a level of sensitiveness not detected by the dose of 0.000,02 mgm.

Incorporation of the Purified Protein Derivative in sterile lactose tablets, in quantities of 0.000,2 mgm. and 0.05 mgm. per tablet, enables a convenient mode of administration of the doses recommended in the preceding paragraph. Repeated comparisons of solutions of the "untableted" and "tableted" Purified Protein Derivative, taken at random from manufacturers' shipments, have shown a high degree of uniformity of the tablets, although an occasional weak reactor to the "untableted" material or to strong Old Tuberculin has escaped detection with the "tableted" Protein Derivative. As the significance of these marginal reactors is debatable, and X-ray studies have failed to show any clinical or a significant proportion of nonclinical tuberculosis among them, no change in dosage is recommended on this account.

With the dosages advocated the majority of reactors in the tests here recorded have fallen in the high two-plus or low three-plus range. Satisfactory sharpness of result has thus been achieved without danger of severe reactions. The dosages indicated are therefore recommended for general use.

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THE PURIFIED PROTEIN DERIVATIVE AS A STANDARD TUBERCULIN[1]

ESMOND R. LONG

The extensive epidemiological studies of tuberculosis, now in progress throughout the world, have made apparent the need for a standard tuberculin. Tuberculin, of one or another type, is in use on a growing scale. With the drop in mortality from tuberculosis, attention is increasingly directed toward another index of the severity of tuberculosis in its community aspects; namely, the incidence of tuberculous infection as determined by the tuberculin test.

In recent publications numerous authors have stressed the variability of tuberculins in present use. Commenting on the increasing use of tuberculin to determine the incidence of tuberculous infection, Opie (1) has said, "Tuberculin varies so widely in strength that it is essential to standardize the sample in use by tests on animals." In presenting data on the new, highly potent Synthetic Medium Tuberculin of the Bureau of Animal Industry, Dorset (2) wrote:

> The power of tuberculin to kill tuberculous guinea pigs has long been used as a measure of potency, but in recent years this has been more or less superseded by the intradermic testing of suitably sensitive guinea pigs. . . . In our experience, neither of these methods enables us to determine with exactness the potency of different tuberculins. Nevertheless either of them will serve, in experienced hands, to bring out *wide* (italics Dr. Dorset's) differences in potency of different tuberculins.

In discussion of this paper by Dorset, Watson (3) recalled the fact that

> Our late, well-remembered colleague, Dr. Schroeder, for many years tested various lots of tuberculins, Bureau tuberculins and commercial tuberculins, and by certain guinea pig tests he classified those either as sub-potent, potent or super-potent, according to results obtained on guinea pigs. But it is quite evident he never disputed it that the potency of the tuberculin classified as

[1] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

potent is not the same as tuberculin classified as super-potent, and that neither one nor the other represents a definite standard.

Watson added a comment of interest in connection with the subject presented in this series of papers:

Now that tuberculin can be produced with a chemically pure medium under the conditions stated by Dr. Dorset, it would seem even possible to look a little further into the future and to visualize the possibility of preparing tuberculins so pure or so separate that one contains the active principle causing the lethal effect and the other only the cutaneous, and to go even further and to be in a position to prepare real, accurate, standard solutions of these tuberculins.

The report of the Tuberculosis Research Committee of the South African Institute for Medical Research makes clear the difficulties encountered in the choice of tuberculin where a large survey of prolonged duration is projected. In the monumental study conducted by this committee it was desired to learn the index of tuberculous infection among laborers entering the Rand and especially to correlate the intensity of their hypersensitiveness to tuberculin with their susceptibility to tuberculosis in the course of their later arduous tasks. For this purpose it was obviously necessary to have a preparation not only of good potency but one of the same potency when supplied to the committee in different shipments. But as the Committee state in their report (4), "There are various tuberculins on the market and, since it was desirable that the same preparation be used throughout, a test was made of the various 'makes' available. . . . Many of the preparations were unsatisfactory, and it was learnt as the result of enquiry overseas that this was a familiar experience."

In England the question has recently been brought into prominence by the addresses and discussion at the Twentieth Annual Conference of the National Association for the Prevention of Tuberculosis (1934). The discussion even led to some notice of the problem in the public press. As quoted by the *London Daily Times*, June 15, 1934, Lord Astor, in referring to the factors accounting for the present reduction in the incidence of tuberculosis, stated that "first of all there were too many brands of tuberculin of different potency on the market;" that "anyone might manufacture tuberculin and offer it for sale, though it might be unsatisfactory;" and that "naturally those tuberculins gave varying, sometimes almost weird, results." Referring to veterinary testing he

went on to suggest that the Government restrict the use of tuberculin for licensed herds to one brand of known potency.

Many similar expressions of opinion could be cited, but enough have been given for illustration of the point.[2] It is interesting to note a growing feeling that standardization is desirable not only to ensure sufficient strength, a fact commonly admitted, but also to prevent overstrength. An experience at the Henry Phipps Institute will illustrate this point. For some years in this Institute a certain preparation, of commercial manufacture, has been employed in clinic use and surveys. It was always potent and appeared reasonably constant in strength. However on a recent occasion a shipment was received that was of greatly increased potency. In the standard first-test dosage used, it produced an unusually high proportion of severe reactions. This event is probably explainable on the basis of observations by Seibert (5), who has found a considerable variation in the quantity of active principle in tuberculin made from different strains of tubercle bacilli and even the same strain under different conditions. Obviously, the use of suitable known quantities of the active principle itself, instead of unknown dilutions of the active principle, would have prevented the untoward result.

VARIATION OF TUBERCULOUS INFECTION THROUGHOUT THE UNITED STATES

Until very recently the statement was frequently made that, although tuberculosis mortality had decreased notably, decline in the extent of tuberculous infection had not occurred. As a matter of fact, however, figures rapidly becoming available from all parts of the country point to a dropping incidence of tuberculous infection, as determined by the tuberculin test, comparable to, if not proportional to the drop in mortality. Among the most reliable figures are those from the Student Health Departments of various American colleges. The figures in table 1 for state universities from the Pacific to the Atlantic coasts illustrate the great variation in infection in the student body of these schools. The figures are based chiefly on tests of the entering class.

The universities selected for comparison draw their student body almost entirely from the region in which they are located, and hence the

[2] Since this paragraph was written Dr. R. A. O'Brien has called my attention to investigations in the Wellcome Research Laboratories (Medical Research Council, Special Report Series, no. 94, 1925, p. 65), showing a difference in potency figure of at least ten times in thirteen samples of veterinary tuberculin examined.

figures represent fairly well the incidence of tuberculous infection at the age and social level of the student body in the states named.

It is evident from the figures that as the east is approached there is a rising incidence of tuberculous infection. This may reasonably be explained on the basis of generally increased liability of contact with cases of tuberculosis in the larger centres of population in the East. The one exception, California, in which a relatively high infection rate for students is recorded, is probably due to an abnormally high infection rate in this state, resulting from the heavy immigration of tuberculous patients in the last fifty years.

All this is highly significant for our understanding of the epidemiology of tuberculosis in America, provided we can be sure of the underlying

TABLE 1

*Tuberculin tests in American universities**

UNIVERSITY	YEAR	DOSAGE OF OT	NUMBER TESTED	PER CENT POSITIVE
		mgm.		
California	1932–3	0.1, 1.0	140	53.6
Idaho	1932–3	1.0	163	25.7
Minnesota	1932–3	0.01, 1.0	11,997	25.2
Wisconsin	1933–4	0.01, 1.0	1,987	28.7
Michigan	1932–4	0.01, 0.1, 1.0	1,073	31.9
Pennsylvania State	1933–4	0.01, 1.0	857	50.3
Pennsylvania	1933–4	0.01, 1.0	896	60.2

* From data furnished by Drs. L. H. Ferguson and H. D. Lees of the Tuberculosis Committee of the American Student Health Association, and Drs. Barnwell and Pollard of the University of Michigan.

basis on which the figures have been collected. These figures are the result of tuberculin testing, and, it must be admitted, we are not sure of their reliability, because the tuberculin used in the different institutions was not the same. Commercial products, products of state laboratories and products of research institutions were employed. As table 1 in the preceding article (Long, Aronson and Seibert) shows, considerable variation in strength occurs in these tuberculins. Hence, unfortunately, we are not sure of the validity of these apparently significant figures.

Actually there is other and indubitable evidence that such differences as the college figures indicate, do exist. The figures assembled in table 2, obtained in surveys by Aronson, Seibert and Long, were secured with the use of a single sample of Old Tuberculin. They indicate definitely

a large difference in the incidence of tuberculous infection at the high-school age in a representative rural county in Michigan, and a typical small town of eastern Pennsylvania.

THE CHOICE OF A STANDARD TUBERCULIN

The essentials of a standard tuberculin are specificity, high potency and constancy. Obviously it must not give false reactions. For satisfaction it must also be sufficiently strong in small dosage to detect cases in which sensitiveness is low. It is necessary also that samples made at different times be of equal strength and that the same sample maintain its original strength. Thus stability as well as potency is demanded. In addition to all of these there is a further requirement, much stressed in recent months. The tuberculin must itself not sensitize the patient in such a way that subsequently positive reactions occur in the absence of tuberculous infection.

TABLE 2

Incidence of tuberculous infection in children of high school age in a rural Michigan county and a small town in eastern Pennsylvania

(Test material OT, same sample; first dose 0.01 mgm., second dose 1.0 mgm.)

AGE-GROUP IN YEARS	MICHIGAN		PENNSYLVANIA	
	Number tested	Per cent positive	Number tested	Per cent positive
10–14	1442	17.6	154	62.3
15–19	378	28.6	169	79.9

The world has an extensive background of reasonably satisfactory usage of Old Tuberculin, and the question naturally arises if Old Tuberculin itself cannot be put on a standard basis. In answer it can only be said that this is hardly possible. Old Tuberculin is not a unit substance, but a mixture of extreme complexity. Its potency is due to about one per cent of its total substance. Ninety-nine parts out of the hundred are inert. Whether, in the ninety-nine parts, there are elements present capable of eliciting nonspecific reactions, is debatable, but obviously the absolute specificity of a tuberculin containing protein derivatives from beef- or milk-peptone cannot be guaranteed. Moreover, in all probability, the actual content of active principle is never twice the same. A glance at the figures given by Seibert (5) on page 719 in table 1 shows that a tuberculin made, for example, from growth of the PN strain of tubercle bacilli might be expected to have two to three times as much active principle as one made in identical manner from H37, and therefore

be that much stronger. In a given dilution the PN tuberculin might, therefore, detect certain weak reactors not discovered by the H37 tuberculin and lead to higher figures than the latter.

It is therefore evident that the only sure way to secure equally potent tuberculins is to make them up from the active principle itself. The question therefore arises if it is possible to secure the active principle in pure form, so that solutions of equal strength can be prepared. The preceding pages of this series of papers have been concerned with the question, but before summarizing their content it seems best to reply to the question, frequently asked, if there is a single active principle. A number of more or less pure substances isolated from the culture filtrate of tubercle bacilli, highly and approximately equally potent in the intracutaneous tuberculin skin test, have been described in recent years. These are all products of protein nature, and, as Seibert (6) has pointed out, the essential difference between them is that of molecular weight. They range from proteins precipitated with ammonium sulphate, like MA100, with molecular weights of approximately 26,000, through products of intermediate molecular size, like TPT, with molecular weights around 8,000, to the Purified Protein Derivative described in this series, with a molecular weight of 2,000–3,000.

A highly significant fact pointed out by Seibert is that the products of high molecular weight readily sensitize animals, so that subsequent intracutaneous injections result in a specific inflammatory response (Arthus phenomenon), while animals repeatedly injected with the product of smallest molecular weight do not become sensitized. She has injected a series of guinea pigs in the Phipps Institute with the Purified Protein Derivative monthly over a period of eight months without evidence of sensitization in the form of significant skin reactions.

A plausible hypothesis on the relationship of these various purified proteins from tuberculin has been given by Seibert.[3] Following the views of Svedberg on the constitution of the proteins, she thinks of the large tuberculin protein molecules as aggregates or polymers of the smaller molecules such as the Purified Protein Derivative described in this series of papers. Whether this particular product is to be considered the actual fundamental unit remains for future research to decide.

Because of their potentiality for sensitizing it seems unwise to use the products of high molecular weight in our present tuberculin campaign,

[3] American Review of Tuberculosis, 1934, xxx, pp. 716–720.

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even though their potency and constancy have been repeatedly established in comparison with samples of Old Tuberculin of known potency. Mariette and his associates (7), Aronson and Nicholas (8) and others have proved the potency of MA100; but Aronson and Nicholas have presented evidence, also, that this product may sensitize children. Lichtenstein (9) and Barnwell and Pollard (10) have established the potency of TPT. The results of the latter investigators are of unusual interest, indicating that TPT will not only detect all cases of tuberculous infection reacting to Old Tuberculin, but a considerable number in addition not reacting to Old Tuberculin, but shown by X-ray to have tuberculous infections. Their argument suggests that TPT uncovers a type of specific sensitivity not detected by Old Tuberculin, and raises the question if it may not have a use in the diagnosis of tuberculous infection. Laboratory experiments (6) have shown that the repeated intracutaneous injection of TPT in relatively large dosage regularly induces skin sensitiveness, but the data of Barnwell and Pollard seem to indicate that the dosages used in human skin-testing do not cause sensitivity.

Until future research has thrown more light on this problem it seems wise to keep our tuberculin campaign in line with the great body of results secured with Old Tuberculin in years past. This is accomplished by isolating the active principle, responsible for the skin test, from Old Tuberculin itself, or a product analogous to Old Tuberculin. The Purified Protein Derivative here described is this substance.

It is much more practical to isolate the active principle from a "product analogous to Old Tuberculin" than from Koch's OT. The separation of the active principle from the constituents of the original culture medium in the latter is practically impossible. On the other hand, it is relatively simple to separate the active principle from a tuberculin made in the same manner as OT, but from a culture-medium of pure crystalloidal constituents, containing no protein, or products of protein nature, before growth of the tubercle bacillus. The isolation and purification of highly potent protein products from Long's synthetic medium have been repeatedly described in recent years in publications emanating from the Committee on Medical Research of the National Tuberculosis Association.

Very recently an important development has made it possible to substitute for Long's medium, for this purpose, a similar medium affording superior growth of the tubercle bacillus and a larger yield of the active principle of tuberculin. This is the medium of the Bureau of Animal

Industry of the United States Department of Agriculture recently described by Dorset (2). A special advantage made possible through the use of this tuberculin is the alignment thus brought about between tuberculin in human use and that employed in the largest and most successful tuberculin project in the world, the cattle-testing program of the United States, sponsored by the U. S. Bureau of Animal Industry. The Purified Protein Derivative described in the accompanying articles is not merely the specific product of Old Tuberculin. It is the specific product of that tuberculin, analogous to Old Tuberculin, employed by the Bureau of Animal Industry in its huge and effective campaign. Dr. Dorset, whose interest and coöperation have always been helpful to the group of investigators working on tuberculin, has made it clear that the Synthetic Medium Tuberculin of the Bureau answers the purposes of the present cattle-testing campaign perfectly. The conditions of human testing are different, in that survey work is commonly less extensive, a much more sensitive skin is involved, and the test may be repeated frequently in the same patient, when a record of the course of sensitiveness over years is desired. The latter factors would seem to warrant the extra effort involved in securing the Purified Protein Derivative from the Bureau tuberculin.

PRODUCTION OF THE PURIFIED PROTEIN DERIVATIVE

The laboratory and manufacturer's production of the Purified Protein Derivative may be briefly summarized from the foregoing articles. The laboratory isolation, as White (11) has brought out in the *Introduction* to these articles, is an outgrowth of studies on the nutrition of the tubercle bacillus first sponsored by the Committee on Medical Research of the National Tuberculosis Association twelve years ago. In these studies synthetic nonprotein media were used as the only media suitable for study of the nutrition and metabolism of the bacillus. A fact, not new but never sufficiently emphasized in previous research, namely, the appearance of protein in the medium as a result of bacillary growth, soon became conspicuous. Further research established the coincidence of appearance of tuberculin activity and protein in the medium, and suitable chemical methods resulted in the isolation of protein of high tuberculin activity (12). Subsequent experiments definitely identified the protein as the active substance. Since 1926 Seibert has steadily improved the methods of isolation and purification, and has reported numerous analytical studies of the products isolated, with the final results described.

As indicated in her paper (5) there are two main steps in the isolation of the Purified Protein Derivative. After a liquid tuberculin analogous to OT has been made from the synthetic medium of the Bureau of Animal Industry by the method described by Dorset (2), it is subjected to the process of ultrafiltration. In the course of this procedure all unutilized constituents of the original medium, as well as metabolites of small molecular size, are filtered off, final traces being removed by the repeated addition of phenolized distilled water in the apparatus. The Purified Protein Derivative, which is a colloid, and a considerable amount of colloidal polysaccharide, inactive in the tuberculin test, remain behind. When free from all substances capable of passing through the membrane of the apparatus, the solution with its colloid content is concentrated by continuing the ultrafiltration, and is then ready for the next step,—precipitation of the Protein Derivative. This is accomplished by the addition of a definite amount of trichloracetic-acid solution. The Protein Derivative is thrown down, and the inert polysaccharide remains dissolved. Repeated washing of the precipitate with a solution of trichloracetic acid removes all except traces of the polysaccharide. The precipitate is further washed with large quantities of ether, which takes away adhering trichloracetic acid and at the same time all moisture, so that a dry powder results. Analysis shows it to be a product of a protein nature, of small molecular weight as compared with whole proteins, free from all original culture-medium constituents, and all metabolites of bacillary growth except a trace of nucleic acid (13). It passes into aqueous solution readily with the aid of a small amount of sodium hydrate, which is neutralized without precipitation of the substance. The solution is a highly active tuberculin. It can be evaporated to dryness *in vacuo* without change. A solution of 5 mgm. in 1 cc. is equivalent in potency to 1 cc. of the particular brand of Old Tuberculin used in the Phipps Institute, which, in turn, as has been shown by comparative tests by Dr. Aronson in this country and Dr. R. A. O'Brien in England, has two to two and a half times the potency of the Old Tuberculin from the Serum Institute of Copenhagen designated as the *International Standard.*

In manufacture on a large scale, the steps are the same, with use of more alundum cups in the ultrafiltration process. The product so obtained can be used in solutions of accurately weighed amounts, or it can be incorporated with a soluble inert substance, like lactose, and made into dry tablets, as described by Clark (14), each containing such

an amount that 0.1 cc. of appropriate solutions delivers the required dose. The use of these tablets appeals to us as obviating many of the difficulties of dilution inherent in the use of OT. There is no need for sterile flasks, pipettes, etc., and the mathematical calculations involved in OT dilution, somewhat confusing and often the cause of errors, are not required. Above all, the material is retained in the dry state, ensuring stability and maintenance of strength.

Throughout the course of its investigation of the various specific products of the tubercle bacillus, the Committee on Medical Research of the National Tuberculosis Association has profited from the active and generous aid of the Mulford Laboratories of Sharp and Dohme and the laboratories of Parke, Davis and Company. These two firms are now coöperating in the production of the Purified Protein Derivative, in conjunction with the Committee on Medical Research. Because of the numerous details involved a special Tuberculin Committee has been set up as a subcommittee of the Committee on Medical Research. Its membership is as follows: Kendall Emerson, Managing Director of the National Tuberculosis Association, Wm. Charles White, Chairman of the Committee on Medical Research of the National Tuberculosis Association, L. T. Clark, representing Parke, Davis and Company, John Reichel representing Sharp and Dohme, and Esmond R. Long, Chairman.

The conditions of manufacture are regulated by this committee. Neither the Purified Protein Derivative nor its process of manufacture is patented, although advantage is taken of an existing patent application in manufacture of the tablets. Under current arrangements the Committee endorses the use of a special designation, namely "Tuberculin, P.P.D. (Purified Protein Derivative)," by these two manufacturing houses, and the sponsorship of the National Tuberculosis Association is limited to their product. Continuous check on the character of the manufactured product is maintained by clinical trial of every lot manufactured, in the Henry Phipps Institute, under the supervision of Drs. Long, Seibert and Aronson.

Among the decisions in the hands of the Tuberculin Committee are those concerning distribution and expense. The cost has been set at the lowest price possible in the present manufacturing state. By action of the Committee the conditions of manufacture and sale of tablets containing the Purified Protein Derivative are defined, and present distribution is limited to the tablets. The way is left open, however, for later distribution of the Protein Derivative in other forms, should such

factors as expense, large-scale usage, etc., warrant. The tablets are obtainable from the manufacturers or their local agents or from the state tuberculosis associations affiliated with the National Tuberculosis Association. The tablets are sold by the state associations at a reduced price, but only in lots of one hundred or more, suitable for survey purposes. The purchase at reduced price carries with it the obligation to submit the results secured to the National Tuberculosis Association for statistical study.

OBJECTIVES IN THE USE OF THE PURIFIED PROTEIN DERIVATIVE

The general objective of any standard is uniformity. In tuberculin testing uniformity is desirable not only for the sake of comparison of single tests on many individuals, but also for comparison of repeated tests on a single person.

The establishment of a standard tuberculin permits the use of a known dose, not possible when solutions of unknown actual strength are the only material available. This dose can be set arbitrarily at a figure calculated to produce sharp but not unduly severe reactions in infected persons of average sensitiveness to tuberculin. It is obvious, furthermore, that the use of a standardized substance must be but part of a standardized process, which ensures uniformity of administration and interpretation of results. In article 5 (Long, Aronson & Seibert) of this series, a fairly extended experience, furnishing a basis for the recommendation of dosage of the Purified Protein Derivative, is presented, and in article 4 (Aronson) definite directions are given for performing the test and reading the results in a standard way.

The immediate objective of uniformity in epidemiological studies should be easily attained with the standard tuberculin here described, as indicated by results in different regions of the country here reported. Up to the present less attention has been paid to the second objective named, extensive and reliable records of tuberculin sensitiveness in individual patients. The reason is that conditions underlying hypersensitiveness to tuberculin are insufficiently known, and varying sensitivity too little understood. One explanation for our lack of information on these vital subjects is the want, in the past, of a constant indicator affording results of reliable comparative value.

It may with good reason be assumed that fluctuations in tuberculin sensitiveness are the result of changes in the extent or character of the infection, or in the constitutional state of the patient. Better knowledge

of the significance of such fluctuations may come through quantitative studies with a uniform test substance, making possible the collection of data of prognostic significance in individual cases. Standardized tuberculin may thus contribute its bit to the theory and practice of medicine in the field of tuberculosis, as well as to the broad field of epidemiology.

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